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The Journal of Allergy

VOL. 6 SEPTEMBER, 1935 No. 6

Original Articles

OBSERVATIONS ON THE NATURE OF THE HOUSE DUST ALLERGEN

MILTON B. COHEN, M.D.,* TELL NELSON, M.D.,† AND
B. H. REINARZ, M.D.
CLEVELAND, OHIO

SINCE Cooke[1] first focused attention on house dust as a cause of asthma, there have been numerous attempts to demonstrate the nature of the active material. On the basis of his observations, Cooke decided that the house dust allergen was a specific substance and that the reaction did not depend on minute amounts of other common allergens present in the dust sample. Rackemann[2] states, "No factor which is common to dust and any other allergen has so far been demonstrated. No other test accompanies the dust reaction invariably."

Our clinical experiences with house dust as the cause of allergic symptoms in man have demonstrated to us that a patient who reacts with symptoms only on exposure to a dust, and gives skin tests and passive transfer reactions to it and to it alone, will react similarly clinically and by test to other samples of dust collected from a variety of sources. For example, a patient from Holland, sensitive to house dust alone, reacts to samples of dust collected in Cleveland, Ohio, Tampa, Fla., Little Rock, Ark., and to dust from her own home in Holland.

The active material is, therefore, widely distributed in nature.

Our own previous experience, as well as that of others, made us suspicious of molds as the active factor. Accordingly, we have tested five patients who react to dust alone with dust collected from various sources in their homes and have submitted the dusts giving positive reactions to Miss A. Piehl, Department of Botany, Western Reserve

Read at the combined meeting of the Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., June 11, 1935.

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†Department of Physiological Chemistry, University of Illinois, College of Medicine.

University, who isolated the molds from these dusts in pure culture. The same patients were then tested with extracts of the molds which had been isolated from the samples of dust from their own homes to which they had given reactions. The following molds were found: *Rhizopus nigricans, Mucor plumbicus, Aspergillus niger,* and several varieties of *Penicillium, Alternaria* and *Monilia.* All these tests with molds were negative. *The active material is, therefore, not a mold.*

The samples of dust which are collected from household articles contain numerous contaminating substances and are not suitable for study of the nature of the active material, since the contaminating materials may influence the results of the experiments. Through the kindness of Dr. Allan Cazort of Little Rock, I obtained a large amount of cotton linters from an unopened bale, extracts of which gave reactions in house dust sensitive patients. The center of this bale could not have been contaminated with any of the common household allergens, and the extracts could contain only the soluble material from cottonseed, cotton fiber, and the house dust. We, therefore, had a source of dust allergen which could be used as a standard for comparison in the following experiments.

Patient L. W. gives a 6+ intradermal reaction to dust and does not react to any epidermals, to cotton, or to kapok. His serum was placed in numbered tubes and was mixed with various extracts. The tubes were kept at room temperature for twenty-four hours, and the mixtures were then used to sensitize sites in the upper arm of three nonallergic persons. Twenty-four hours later the sensitized sites were tested in accordance with Table I.

TABLE I

NEUTRALIZATION TESTS WITH SERUM CONTAINING REAGINS TO HOUSE DUST AND VARIOUS ALLERGENS

TUBE 1	TUBE 2	TUBE 3	TUBE 4		
Serum 2 parts Diluent 1 part	Serum 2 parts Stock dust 1 part	Serum 2 parts Linters dust 1 part	Serum 2 parts Cottonseed 1 part	TEST SUBSTANCES	
+++	0	0	++	Dust (stock)	
0	0	0	0	Cottonseed	Recipient 1
0	0	0	0	Dog	
0	0	0	0	Feathers	
0	0	0	0	Horse	
++++	0	0	++	Dust (linter)	Recipient 2
+++	0	0	++	Dust (linter)	Recipient 3

This experiment shows conclusively that the allergen contained in the linters dust extract will neutralize the antibodies in the serum of a dust sensitive patient and that the *active material is not a common antigenic substance.* This type of experiment has been repeated with serum from three other dust sensitive patients with entirely similar results.

Patient D. R. gives a 2+ scratch test to cottonseed but does not react to house dust. His serum was tested after mixture with various extracts in the skin of three normal persons in a manner identical with that described above with results as shown in Table II.

TABLE II

NEUTRALIZATION TESTS WITH HOUSE DUST, LINTERS AND COTTONSEED. SITES TESTED WITH COTTONSEED

TUBE 1	TUBE 2	TUBE 3	TUBE 4	TEST SUBSTANCE
Serum 2 Diluent 1	Serum 2 Dust (stock) 1	Serum 2 Linters dust 1	Serum 2 Cottonseed 1	
+++	++	++	0	Cottonseed

This experiment shows conclusively that the reacting material in the linters extract is not the cottonseed. It seemed desirable to check these findings by precipitin tests with various solutions used for skin testing, and attempts were made to immunize rabbits with a purified extract of this cotton linters after adsorption on aluminum cream. Animals injected with antigens prepared in this manner give good precipitin titers. The animals treated with the linters preparation, however, did not develop precipitins and in vitro experiments could not be performed.

Through the kindness of Dr. Lewis Abram of Fitzgerald, Georgia, we obtained a large box of fresh cotton linters from the 1934 cotton crop. Extracts of these linters gave negative reactions on ten house dust sensitive patients. Portions of these linters were placed in jars or flasks and treated as follows:

Jar 1. Open to air.

Jar 2. Open to air filtered through cotton.

Jar 3. Autoclaved at 120° C. for one hour, open to air, filtered through cotton.

Jar 4. Sealed.

Jar 5. Autoclaved at 120° C. for one hour in sealed jar. All jars were placed on a laboratory shelf Sept. 27, 1934. At various times during the winter and spring samples of Jar 1 were extracted and tested on dust sensitive patients. On May 7, 1935, saline extracts of the linters in Jar 1 gave good intradermal reaction in dust sensitive patients and none on normal skins. All jars were opened on May 8; extracts and tests were made with the results shown in Table III.

All samples gave positive reactions in some of the patients. In general the reactions were larger in the samples with free access to air. The reacting material neutralizes serums from house dust sensitive patients. A consideration of these results demonstrates that the active material in dust cannot be a mold or other living substance, since the autoclaved jars developed activity. It is not a contaminat-

ing substance from outside the jars, since it occurred in those which were sealed. The evidence suggests that the house dust antigen is some degenerative product of cotton linters, in this instance. Experiences with the reactivity of old feathers and kapok as compared to

TABLE III

INTRADERMAL TESTS WITH EXTRACTS OF COTTON LINTERS TREATED IN VARIOUS WAYS

	JAR 1 OPEN TO AIR	JAR 2 OPEN TO AIR FILTERED THROUGH COTTON	JAR 3 AUTOCLAVED 120° C. ONE HOUR OPEN TO AIR, FILTERED THROUGH COTTON	JAR 4 SEALED	JAR 5 AUTOCLAVED 120° C. ONE HOUR SEALED ONE HOUR
Patient 1 D. S.	6+	6+	4+	4+	4+
Patient 2 D. S.	2+	2+	+	±	±
Patient 3 D. S.	+	+	+	+	+
Patient 4 D. S.	+	+	+	0	0
Patient 5 Neg. Reactor	0	0	0	0	0
Patient 6 D. S.	5+	2+	2+	3+	2+
Patient 7 D. S.	+	2+	+	0	0
Patient 8 D. S.	2+	2+	2+	2+	2+
Patient 9 D. S.	+	+	±	0	±
Patient 10 D. S.	3+	3+	3+	3+	3+

D.S. = Dust sensitive.

that of new materials suggest that a similar product develops during the aging of these substances. Experiments are in progress to determine these points.

CONCLUSIONS

1. House dust allergen develops in cotton linters under conditions which exclude the possibility of contamination with other common allergens.

2. The development of house dust allergen in cotton linters is not dependent on bacterial or mold action on the linters.

3. The active allergen is not a mold.

4. It is probable that the house dust allergen is developed during the aging process in cotton linters and probably in other substances such as feathers and kapok.

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2. Rackemann, F. M.: Clinical Allergy—Asthma and Hay Fever, New York, 1931, The Macmillan Co.

DISCUSSION

DR. R. A. COOKE, New York.—This is a study of considerable interest to all of us. After it was first demonstrated that there was an active substance in house dust, many of us spent hours of time and

thought trying to find the source or the nature of the active allergen. Frankly, up to the present time, as Dr. Cohen has said, there has been no real light thrown upon this subject. It would seem to me, from the presentation which he has made here this afternoon, that he is probably now on the verge of the discovery of its source, and more power to him in the continuance of this investigation. I am sure he will have something more to report to us next year. It is a very important work and is going to be of great value to all of us in the management and treatment of these cases.

DR. CHARLES N. HENSEL, St. Paul.—It seems that on this problem of sensitization to house dust, Dr. Cohen has given us an interesting lead that we should all go on with and develop further. There is another phase of the house dust problem that I have encountered, namely, sensitization to the insulating pads under carpets and rugs, which are made of cattle hair. This insulating material is called Ozite.

It was only through chance that I discovered this cattle hair factor. I had a patient with an allergic nasal condition who was sensitive to feathers and animal hair, including cattle hair, as well as many allergens. One morning his wife was cleaning the floors, and the rugs were turned back, and she noticed red hairs in the padding under the rug. She inquired of the store in which the pads were purchased as to the composition of this material and was told that it was cattle hair. I got in touch with the manufacturers of this floor insulator and learned some interesting facts concerning its manufacture.

In the process of tanning leather, the hair has to be plucked out, and this had always been discarded as a useless by-product to be dumped into the river or in vacant lots or abandoned quarries. Finally the Health Department in various localities felt that this material was a health hazard and that it should be disposed of in some other way.

About six years ago a trust was formed involving most of the leather manufacturers of the United States, and they employed a research chemist to see whether this waste hair could not be utilized in some way. A process was found for cleansing the hair and then making it into felt pads by the use of great pressure which caused the hairs to adhere and gave the pads a certain amount of resiliency.

As a final step in the manufacture long rolls of this padding material were placed in large rooms, draped over racks, and for three days were supersaturated with ozone with the idea of sterilizing the pads and on the theory that the increased oxygen would harden the hairs so that they would become nonirritating to human beings.

They had now produced something salable out of material that formerly had been discarded as waste, but there was no market for this product; so a market had to be created by a national advertising campaign. As a result of this advertising, the stores pushed this product, people came to like it, and now it has come to be commonly used in a majority of homes. Therefore in testing house dust sensitive patients, we should include the use of cattle hair extracts even though the individual may be a city dweller and does not come into contact with cattle.

In order to determine whether the ozoning process would destroy the allergic factor in manufactured Ozite, I had extracts of Ozite

made, and skin tested this patient with both Ozite extracts and the cattle hair extracts. The patient reacted positively to both extracts, and the reactions were equal in intensity. Therefore, it was obvious that Ozite was just as active an allergen as was cattle hair. This fact was confirmed clinically because the patient repeatedly found that his nasal symptoms were aggravated Saturday and Sunday when he spent much of the time in the house. His wife also recalled that when they had moved into the house five years before, for the first time in their housekeeping arrangements their rugs were insulated with Ozite padding, and most of the patient's nasal symptoms dated from that time.

Since the patient did not wish to discard all this insulating material, an attempt was made to desensitize him with extracts of cattle hair. This attempt was only partially successful, and finally the Ozite padding was removed, and jute padding was substituted because the patient was not sensitive to jute extract. He is now much more comfortable.

Following this experience I encountered two other patients who were sensitive to cattle hair and whose nasal symptoms were aggravated when they occupied rooms containing Ozite padding. I would suggest, therefore, that all house dust sensitive individuals be tested with cattle hair extracts.

Dr. Samuel M. Feinberg.—I think Dr. Cohen's observations are more far-reaching than he will admit. If, as he says, aging cotton will produce an antigenic substance, aging feathers will do the same thing, then why not aging vegetation, decomposing bacteria, and other organic material of every type—leaves, and so forth? I cannot believe these three substances are vitally different from a great many other organic substances. I am not denying his conclusions, but I am wondering whether he has not hit on something much more important, whether he has not found or pointed the way to something for which we have been looking a long time—the unknown factor in a great many patients who are sensitive to something we cannot discover.

One other point I should like to raise. I am told by some physiologists that heating, such as Dr. Cohen describes, to 123° C. for an hour will destroy all enzymes. Unless these enzymes which break down this cotton are unusual, we cannot very well explain it on that basis.

Dr. J. A. Rudolph, Cleveland.—Both Dr. Cohen and I have written observations made on dust asthmatic persons. Most of the antigenic substances were found to be in bedding, upholstery, upholstered furniture, and overstuffed pieces of various types. I have been interested in this antigenic dust, because I found my patients not sensitive to substances, such as kapok, cotton or feathers, but yet to dust from the sources mentioned above. I do not feel that the dust antigen is quite so elusive a substance as one may be led to believe.

In an investigation of patients sensitive to dust, the following facts were learned and may be in the nature of a clue to the real substance in dust which is responsible for some of the clinical allergies.

In the better grades of tickings used in making mattresses, box spring covers, pillows, etc., such as those required for government

specifications, only the warp yarn is sized. This sizing consists primarily of three elements: first, starches or adhesive substances; second, softening substances to preserve the pliability of yarn during weaving; third, antiseptics that tend to destroy microorganisms and prevent growth of mildew. The material used in the "first" is usually cornstarch. That used in the "second" is tallow, which contains oleic and steric acid, as well as some glycerin. Other softeners are made from sulphonated castor oil and palm oil. "Third" may be a variety of substances, including some of the phenol derivatives, and commonly zinc chloride. The composition of the sizing itself is about 90 per cent starch, 9½ per cent softener, and 0.5 per cent antiseptic, but of this mixture only about 8 per cent of the weight of the warp yarn is applied as sizing. Since filling is unsized, it means about 5 per cent of the weight of the fabric.

In some of the lower grades of ticking, the goods are sized after weaving, in which case the elements of sizing vary, and may include dextrins, gums, softening, and sometimes china clay.

In a later report, a listing of the above substances will be given with their various reactions on patients as compared with our stock dust antigen.

DR. BRET RATNER, New York.—Dr. Cohen's paper is extraordinarily interesting, particularly in the instance of the individual who reacted to the linters and not to the cottonseed. We have all had the experience of not being able to ferret out the exact causative agent in asthmatic cases.

Seven years ago I began to test my patients, all children, with substances obtained from the immediate environment. Finding negative results from tests with stock feather proteins, cottonseed, and epidermals in general, I was agreeably surprised to get positive reactions with proteins obtained directly from the environment of the patient. To make the problem a little more concrete, every patient who comes to me, after being tested with all the available stock proteins, is tested with extracts from practically every dust producing article, samples of which the mother is willing to collect. One patient brought as many as 136 samples. We did not make elaborate extracts of these substances, but merely soaked a bit of the sample in a small amount of N/100 KOH. After a scratch on the skin, these extracts were placed thereon. The results in the case cited—and I could mention others if time permitted—were very striking. There were 35 positive reactions to various substances, all of which contained cotton linters, in spite of the fact that this child had given a negative reaction to cottonseed protein. The finding in this case is consonant with the reactions Dr. Cohen obtained with the old linter extract. After removing some of the offending articles, and carefully covering others to make them as nearly dust proof as possible, the child went along without any asthmatic attacks for many months. In a history course in school, however, the children were taught the making of cotton cloth, and this child, along with three other children in the same school who happen to be my patients, got severe attacks of asthma. Then more than a year later the following episode occurred. The first night in their country home, the child slept in the garage,

as the house was not entirely cleaned and ready. The child developed an asthmatic attack. The mother searched the garage and found a large nest the mice had made of cotton linters.

In my practice I can say that without testing every patient with eczema and asthma with many environmental substances I am sure that my results would not be quite so good. Dr. Cohen's extract may well serve as a short cut.

DR. COHEN.—Dr. Hensel, there is no kapok here. We started with patients who reacted to house dust alone. We test with cattle hair routinely. I agree with you that Ozite is the cause of difficulty in some of these patients, although it has no bearing on this point.

Dr. Feinberg, I do not know what other things there may be that will do this. Perhaps you are right that a lot of other things will. I do not want to indulge in any wish fulfillment thinking about it, so I shall wait until we can write Q. E. D. after it. I know nothing about enzymes, so I cannot give you any answer.

Dr. Ratner, as far as these experiments are concerned, when you take cotton linters that are never exposed to anything else and seal up the jars, they cannot become contaminated with any of these substances.

DIPHTHERIA IMMUNIZATION OF ALLERGIC AND NONALLERGIC INDIVIDUALS BY INTRACUTANEOUS INJECTION OF ALUM-PRECIPITATED TOXOID*†

RICHARD A. KERN, M.D., JEAN CRUMP, M.D., AND THOMAS A. COPE, M.D.
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FROM time to time there are encountered individuals who suffer severe general reactions upon being given injections of toxin-antitoxin, toxoid, or alum-precipitated toxoid for the production of an active immunity against diphtheria. It has been our experience that such reactions are seen much more frequently in allergic than in nonallergic persons. If in such a case the first injection fails to produce an adequate immunity as shown by a negative Schick test, it is often difficult to convince an adult patient or the parents of a reacting child that further injections should be hazarded until the Schick reaction becomes negative. Particularly was this true when three doses of toxin-antitoxin were the usual method of inducing active immunity to diphtheria. The following is a case in point:

CASE 1.—R. R., a boy aged two years, and a sufferer from asthma, was given a dose of toxin-antitoxin June 1, 1933. The child promptly developed urticaria and a most violent attack of asthma. The parents refused to have any further injections given. On Nov. 17, 1933, the Schick test remained strongly positive. This child was not sensitive to horse dander or horse serum.

The introduction of alum-precipitated toxoid for the production of active immunity against diphtheria was an important improvement. Alum-precipitated toxoid contains no animal serum that might induce hypersensitiveness or that might shock a hypersensitive patient. It is insoluble and is therefore absorbed only very slowly, making severer types of reactions far less likely. A single dose usually suffices to immunize.

Nevertheless, severe general reactions are at times encountered after its use. As with other methods of diphtheria immunization, reactions are more often seen in adults. Again, we have observed such reactions more frequently in allergic individuals. A recent example in our experience is the following:

CASE 2.—M. R., a medical student, twenty years of age, subject to gastrointestinal symptoms on eating foods to which he is sensitive, and whose sister suffers from hay fever, received a subcutaneous injection of 1 c.c. of alum-precipitated toxoid.

*From the Allergy Section of the Medical Division of the Hospital of the University of Pennsylvania and the Allergy Clinic of St. Christopher's Hospital.

†Read before the combined meeting of the Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, June 10, 1935, in Atlantic City, N. J.

That evening he developed urticaria, headache, and abdominal cramps. The following day there were marked swelling of the face and hands, marked itching, and fever. There was also a marked flare-up at the site of a former Schick test. Symptoms slowly subsided in the course of three days.

There would appear to be a need, therefore, for an effective immunization method that is less likely to produce unfavorable reactions, especially in allergic subjects.

It is an established fact that the skin plays an important part in the production of immune substances. The intracutaneous injection of a given quantity of an antigen will evoke the production of immune substances in amounts that would require a much larger subcutaneous or intravenous dose to call forth. Thus in 1930, Tuft,[1] reporting before the Society for the Study of Asthma and Allied Conditions his observations on agglutinin production after typhoid vaccine injections in human subjects, showed that small doses of typhoid vaccine given intracutaneously produced a better response than larger doses by other routes. In closing the discussion of his paper at that time, he said that he had observed a Schick test becoming negative as a result of small intracutaneous toxoid injections.

It therefore occurred to us that an intracutaneous dose of a small amount of alum-precipitated toxoid might be equally as efficacious as a larger subcutaneous dose in producing active immunity to diphtheria by a single injection, and at the same time would be less likely to induce severe local or general reactions, especially in the allergic patient.

TABLE I

IMMUNIZATION RESULTS IN NONALLERGIC PERSONS RETESTED SIX WEEKS AFTER INJECTION WITH A SINGLE DOSE OF ALUM-PRECIPITATED TOXOID

METHOD OF INJECTION	DOSE	NUMBER OF CASES*	RESULT OF SCHICK RETEST	
			NEGATIVE	POSITIVE
Intracutaneous	0.05 c.c.	24	11	13
Subcutaneous	0.5 c.c.	25	15	10

*All adults.

The first point to be investigated was to see whether one could achieve a negative Schick test by a single intracutaneous injection of alum-precipitated toxoid in a dose much smaller than that required, when given subcutaneously, to produce such a result. The intracutaneous dose selected was 0.05 c.c. of a preparation of which the subcutaneous dose was 0.5 c.c. The subjects were 49 medical students with positive Schick tests. Twenty-four received an intracutaneous injection of 0.05 c.c. on the outer aspect of the upper arm, and the other 25 were given 0.5 c.c. of alum-precipitated toxoid subcutaneously. For reasons beyond our control, it was necessary to retest the subjects only six weeks after the immunizing dose, a time that is obviously too

short. It is well recognized that in any diphtheria immunization procedure it will usually take at least three months to achieve immunity, and that at least three to six months should be allowed to elapse before retesting. Nevertheless 11 of the 24 subjects receiving the small intracutaneous dose had a negative Schick test after six weeks. This was proof that it was possible to produce immunity by a single small intracutaneous dose of the antigen.

In a second group of 33 nonallergic persons with positive Schick tests it was possible to let six months elapse between the immunizing dose and the retest. Eighteen subjects, including 14 student nurses and 4 children, were given an intracutaneous injection on the outer aspect of the upper arm of 0.1 c.c. of another preparation of alum-precipitated toxoid, of which the subcutaneous dose was 1.0 c.c. The other 15 subjects, 9 nurses and 6 children, received 1.0 c.c. subcutaneously. It will be seen from Table II that the results of intracutaneous injection were even a little better than those after subcutaneous injection.

TABLE II

IMMUNIZATION RESULTS IN NONALLERGIC PERSONS RETESTED SIX MONTHS AFTER INJECTION WITH A SINGLE DOSE OF ALUM-PRECIPITATED TOXOID

METHOD OF INJECTION	DOSE	NUMBER OF CASES	RESULT OF SCHICK RETEST	
			NEGATIVE	POSITIVE
Intracutaneous	0.1 c.c.	18 (4)	13 (2)	5 (2)
Subcutaneous	1.0 c.c.	15 (6)	10 (3)	5 (3)

Figures in parentheses give the number of children which the other figures include.

The next group to be reported includes 53 allergic individuals with positive Schick tests, only one of the group being an adult. All were seen in our clinics because of obvious allergic disease; all but one had a family history of allergy, and the 50 who were tested were all found sensitive to various atopens.

An intracutaneous injection of 0.1 c.c. of alum-precipitated toxoid was given to 41 of this group, including the one adult. Three to six months later, 32 had negative Schick tests, a proportion of successes that is quite as good as that obtained in practice by any other method of immunization. It is interesting to note that in 4 of these children unsuccessful attempts at immunization had previously been made: two had received 3 injections of toxin-antitoxin; one had been given one dose and the other two doses of toxin-antitoxin, but further injections had been refused because of severe general reactions. All 4 had negative Schick tests after the single intracutaneous dose of 0.1 c.c. of alum-precipitated toxoid.

The other 12 allergic children were given a single subcutaneous dose of 1.0 c.c. After three to six months 10 had negative Schick tests.

The same lot of alum-precipitated toxoid was used in all cases except the subjects referred to in Table I.

TABLE III

IMMUNIZATION RESULTS IN ALLERGIC PERSONS RETESTED THREE TO SIX MONTHS AFTER INJECTION WITH A SINGLE DOSE OF ALUM-PRECIPITATED TOXOID

METHOD OF INJECTION	DOSE	NUMBER OF CASES	RESULT OF SCHICK RETEST	
			NEGATIVE	POSITIVE
Intracutaneous	0.1 c.c.	41*	32*	9
Subcutaneous	1.0 c.c.	12	10	2

*Includes one adult.

It would seem, then, that the intracutaneous single injection of one-tenth of the usual subcutaneous dose of alum-precipitated toxoid is quite as effective as the full subcutaneous single dose in producing active immunity against diphtheria. Furthermore, allergic subjects respond as well as, if not better than, nonallergic individuals.

Turning now to the matter of unfavorable reactions, local and general, our observations are summarized in Table IV.

TABLE IV

UNFAVORABLE REACTIONS FOLLOWING INJECTIONS OF ALUM-PRECIPITATED TOXOID

METHOD OF INJECTION	NUMBER OF CASES	LOCAL REACTION MARKED	GENERAL REACTION	
			SLIGHT	MARKED
Intracutaneous	88	6	5	2
Subcutaneous	54	13	4	6

Alum-precipitated toxoid is an insoluble substance. Its injection, whether into or under the skin, is followed by a sharply defined firm nodule about the size of the quantity injected. This nodule slowly grows smaller as the material is absorbed and finally disappears, on an average, in six weeks. In practically all instances there results a slight reactive inflammation around the injected material, adding slightly for a few days to the size of the nodule and, in case of intracutaneous injection, with a zone of erythema around the nodule to a radius of about 1 cm. The nodule is slightly tender, but on the whole this reaction is trifling.

At times, however, there is a more or less marked local reaction, with considerable redness, swelling, tenderness, and discomfort. General reactions may also occur, either with or without a marked local reaction. When a patient complained of malaise and achiness or when there was loss of appetite, but without fever, the general reaction was recorded as slight. When these symptoms were exaggerated and attended by fever, the general reaction was recorded as marked.

It will be seen from Table IV that intracutaneous injections were followed by distinctly fewer reactions, both local and general, than

were subcutaneous injections. This difference was particularly marked in adults, as will be seen in Table V.

TABLE V

UNFAVORABLE REACTIONS FOLLOWING INJECTIONS OF ALUM-PRECIPITATED TOXOID, WITH REFERENCE TO AGE OF SUBJECTS AND METHOD OF INJECTION

SUBJECTS	INTRACUTANEOUS INJECTION				SUBCUTANEOUS INJECTION			
	NUMBER OF CASES	MARKED LOCAL REACTION	GENERAL REACTION		NUMBER OF CASES	MARKED LOCAL REACTION	GENERAL REACTION	
			SLIGHT	MARKED			SLIGHT	MARKED
Children	39 (46)	2	0	0	30	1	0	1
Adults	40	4	5	2	33	12	4	6

Figures in parentheses represent number of injections which these 39 patients received, including 6 second injections and 1 third injection.

Marked reactions, both local and general, in adults occurred more than three times oftener after subcutaneous than after intracutaneous injection. A marked general reaction was observed only once in a child, and this was after subcutaneous injection. Of the two marked local reactions recorded after intracutaneous injection in children, one was really an infection, due evidently to an error in technic.

The question comes up, whether general or local reactions would be more likely to result if an intracutaneous injection had to be repeated, or if it had been preceded by other attempts at diphtheria immunization. Of the 4 children who had previously received one or more injections of toxin-antitoxin, none experienced a general reaction and one had a marked local reaction. The latter child had been given 2 doses of toxin-antitoxin a year before, at which time he had had a severe general reaction. Of the 9 children who still had a positive Schick test after the first intracutaneous dose of alum-precipitated toxoid, 6 were given a second intracutaneous injection of 0.1 c.c. without either a marked local or a general reaction; three months later 4 were Schick-negative, one was still Schick-positive, and one did not return for testing. The one Schick-positive child was given a third intracutaneous dose of 0.1 c.c., again without reaction and this time became Schick-negative.

Of 7 adults who had previously received toxin-antitoxin, 2 had reactions (one local, and one local and general) after intracutaneous alum-precipitated toxoid. Three of another 7 such adults had reactions (one local, and two local and general) after subcutaneous alum-precipitated toxoid. Reactions appear to be more frequent in those who previously had toxin-antitoxin injections, more frequent in adults, and more frequent in those given subcutaneous than in those given intracutaneous alum-precipitated toxoid.

It is here noted that Tables IV and V record a larger number of subjects than are included in the previous three tables, because a

number of patients failed to return after the three to six months for the Schick tests.

An interesting observation was made in the one allergic adult who became Schick-negative after a single intracutaneous dose of 0.1 c.c. of alum-precipitated toxoid. This patient, a woman of twenty-eight years, in addition to having grass and ragweed hay fever, was highly sensitive to feathers, horsehair, cat hair, orris root, and a number of foods, with resultant urticaria and allergic rhinitis. Her first Schick test was strongly positive, but not otherwise remarkable. When the second Schick test was performed three months after the intracutaneous immunization, there was, however, an immediate local reaction at the site of the test with a wheal, and with redness and swelling that involved the whole forearm. The next day this was completely gone, and at forty-eight and seventy-two hours the Schick test was clearly negative. The control test, with heated toxin, performed at the same time on the other arm showed no reaction whatever. These observations would suggest that this patient had become sensitized to diphtheria toxin.

The implications of the observations here reported are more extensive than may at first be apparent. Our findings confirm and extend the observations of Tuft on the efficacy of the intracutaneous method of immunization as well as its lesser likelihood to provoke unfavorable reactions. They suggest that the intracutaneous route should be preferred for active immunization against diphtheria, especially in allergic subjects. But what may prove equally or more important, they suggest the possibility of extending this method to other fields of immunization: notably to tetanus and scarlet fever.

Every allergist has had the uncomfortable experience of being asked to administer tetanus antitoxin to an allergic child with a possibly infected puncture wound. If the allergic child could be actively immunized against tetanus, it would perhaps obviate the need for such tetanus antitoxin injections. We are therefore engaged in studies on such active immunization with an alum-precipitated tetanus toxoid.

SUMMARY

1. A single intracutaneous injection of alum-precipitated toxoid is as successful as a subcutaneous injection in producing active immunity against diphtheria, and with a dose only one-tenth of that usually employed in the subcutaneous method.

2. Intracutaneous diphtheria immunization is distinctly less likely to produce unfavorable reactions, local or general, than is the subcutaneous method.

3. Intracutaneous diphtheria immunization with alum-precipitated toxoid should therefore be the method of choice, especially in allergic subjects.

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DISCUSSION

DR. TUFT, Philadelphia.—This presentation is of particular interest to me for two reasons: first, because it again brings out the importance of the skin in relation to immunity, and second, because Dr. Kern and his coworkers were able to accomplish in much better fashion something which I did not succeed in doing several years ago. In the spring of 1931, my associate, Dr. Wenger, and I were engaged in actively immunizing the students of the Temple University Medical School against diphtheria. Injections of toxoid in the usual fashion were productive of similar severe reactions as described by Dr. Kern. We therefore tried to avoid this by splitting the dose into 5 parts and giving these subcutaneously; but this was likewise productive of reactions. It occurred to me, in view of my experience with typhoid vaccine given intradermally, that it might be possible to give the toxoid intradermally and avoid reactions. Accordingly we divided the Schick-positive group into two groups—the first group of 18 persons received 5 doses (0.1, 0.25, 0.5, 1.0, and 1.5 c.c. respectively) of the concentrated toxoid subcutaneously at weekly intervals; and the second group of 24 persons received 4 doses (0.05, 0.1, 0.15, and 0.2 c.c. respectively) of a diluted toxoid (1:100) intradermally. I used a diluted toxoid because of fear of irritation and reaction from the concentrated preparation. Schick tests were performed three months later—17 of the first group gave negative reactions, a percentage of 94.4 per cent, whereas in the second group only 14, or 41.7 per cent, were negative. Practically no reactions occurred after the intradermal administration. From the presentation of Dr. Kern, it is evident that our error consisted in employing a diluted toxoid instead of the concentrated preparation. At present, of course, the alum-precipitated toxoid offers an additional advantage. I believe that this method may be particularly useful in the immunization of adults in whom the administration is much more liable to be followed by disagreeable reactions.

STUDIES IN ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS*†

V. A New Technic for Quantitatively Studying the Absorption and Elimination of Antigens (Preliminary Report)

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ABOUT ten years ago one of us (M. W.)[1] described a *direct* method for demonstrating the absorption of unaltered protein in human beings. The technic was immunologic in nature and made use of human serums of extremely high reagin content which were obtained from atopic patients, who were markedly sensitive to certain foods. Normal subjects were passively and locally sensitized with an intracutaneous injection of about 0.05 c.c. of such a serum and, on the following morning, were fed the related protein. The onset of a reaction at the sensitized site, usually within several minutes, marked the entrance of the unaltered protein into the circulation.

The above experimental principle was also employed by us in our investigations on the nature and mechanism of wheal formation.[2, 3] During the course of these studies one of us (A. W.) devised a variation in the routine experimental technic, which consisted of feeding the antigen before local passive sensitization is performed. In one of our earlier publications on urticaria[3] we mentioned the type of wheal produced by this modified technic. We also pointed out its possible use in quantitative studies on the absorption of unaltered protein. Further improvement of the technic now warrants its presentation as a practical *direct* method for tracing the rise and fall of the antigen tide in the blood stream. This technic will be referred to as the "reverse" technic because of the fact that the sensitization is performed *after* the absorption of the antigen rather than *before*, as in the original method.

Most of the present studies were made with a serum containing reagins for peanuts in high concentration. Egg and fish serums were also used. These serums could passively sensitize the skins of nonatopic subjects in dilutions of 1:1,024 or higher.

For passive local sensitization in the reverse technic approximately 0.01 c.c. of sensitizing serum was used for intracutaneous injection. Some serums were used in dilutions up to 1:10.

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†Read at the combined meeting of the Society for the Study of Asthma and Allied Conditions and the Association for the Study of Allergy, Atlantic City, N. J., June 10, 1935.

The peanut test meal consisted of 20 or 40 slightly roasted peanut kernels (about 15 or 30 gm.). For the egg meal, one or two egg whites were taken. The fish meal consisted of 50 gm. or about one-third of a raw herring. About 15 c.c. to 30 c.c. of water were allowed with the test meal.

The subjects were all normal nonatopic adults. The antigenic foods which were employed in these tests were excluded from their diets for at least forty-eight hours before the experiments were begun. All tests were done in the morning on a fasting stomach. The outer and anterior aspects of the arms and the flexor surface of the forearms were the areas utilized for passive sensitization.

The normal cutaneous response of each subject to the injection of the sensitizing serum was determined by an intracutaneous test with the serum one-half an hour before the test meal. If a local reaction resulted, its size was noted. In most instances, such reactions were very slight and disappeared rapidly.

The subject was then fed the test meal. The onset of a reaction at the site which had been injected one-half hour previously marked the entrance of the ingested protein into the circulation. This usually occurred from five to thirty minutes after the test meal. The time of onset and the intensity of the reaction were noted. Measurements of the wheal and erythema were taken at ten- and twenty-minute intervals after the onset of the reaction.

After the entrance of the protein into the circulation, sensitizing injections of the serum were repeated every thirty minutes. Later, the intervals were increased to an hour or more. In a number of instances the injections were done in duplicate in order to study the degree of variation obtained with this technic.

About eight or ten minutes after each sensitizing injection of the serum, a reaction started which could easily be differentiated from the normal response of the skin to the serum. Pruritus, erythema, and wheal developed rapidly. In most cases the reactions were complete within twenty minutes after the injection. Measurements of the wheal and erythema at this time varied from 3 mm. to 7 mm. and from 0.6 cm. to 2.5 cm. respectively.

The largest reaction obtained with the reverse technic usually developed during the first two hours of absorption of the offending food. Subsequent reactions decreased progressively in size and intensity. By charting the degree of the successive reactions as measured by the size of the wheal at twenty minutes, a curve can be drawn, which graphically represents the tide of the antigen in the circulation. In Chart 1, the antigen tide in a normal subject is traced for the first eight hours following the ingestion of a test meal of 40 peanut kernels. In Chart 2 it is traced for approximately forty-eight hours in another

subject following a meal of 20 peanut kernels. With this antigen, the curve in most subjects shows a sharp rise which reaches its maximum from one-half to two hours following ingestion of the meal. Then follows a rather rapid fall for six or eight hours, with a subsequent more gradual and prolonged decline lasting from sixteen to thirty hours. In most subjects tested with peanuts under the conditions outlined above, the antigen could not be detected after forty-eight hours.

About forty-eight hours after the subject had received the last injection, he was again fed the same test meal. From five to sixty minutes later, reactions appeared again at some of the old sites. It was noted that the sites at the end of the series which had reacted the least or not at all with the reverse technic, now lit up first and with the

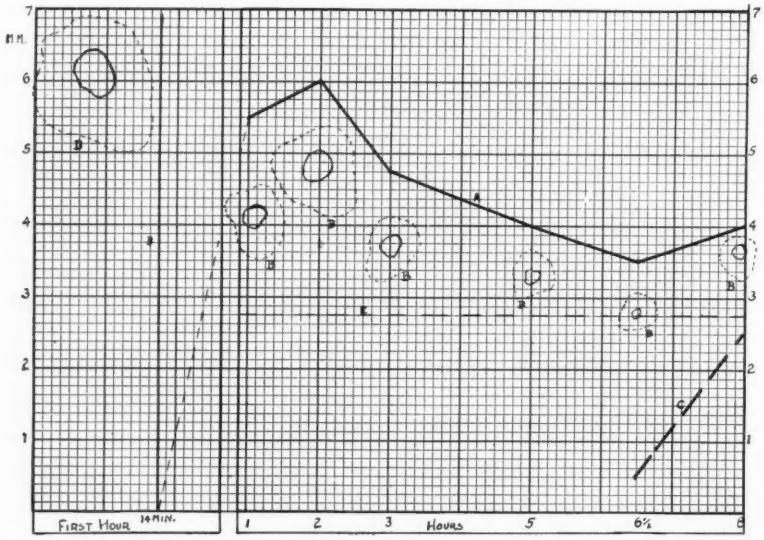

Chart 1.—Antigen tide in C. E. H. after ingestion of 40 peanuts as traced by the reverse technic, and curve on second feeding of antigen. Serum testing strength 1:4.

A, reverse technic curve.

B, wheals by the reverse technic.

C, second feeding curve.

D, ingestion (direct technic) wheal. size, and time of onset.

E, indicating size of cutaneous response to serum before ingestion of peanuts.

largest wheals. The sites preceding these in time of sensitization showed progressively diminishing reactions and were slower in appearing. Those at the beginning of the series at which the largest reactions had been obtained by the reverse technic gave practically no response on the second feeding of antigen. This series of reactions, when plotted graphically according to size, forms another curve which, for the most part, is the exact opposite of that obtained originally on the same sites (Chart 2). The reason for this is obvious. With the reverse technic, each successive site, after the first hour or two, becomes the seat of a smaller reaction than its predecessor, as a result of the

decreasing amount of the antigen in the circulation. For the same reason, an increasing amount of unneutralized reagins remains deposited at each successive site. Hence at the subsequent ingestion of the antigen, the largest wheals form at those sites which have previously reacted the least, and vice versa. The value of the second curve is that it may be employed to confirm the findings of the first. The principle involved in the second feeding curve is similar to that employed by Cohen and his coworkers[4] to estimate "the disappearance time of circulating ragweed pollen material after absorption from the nose and throat." In their studies, passive sensitization was performed only at twenty-four-hour intervals for three days, and no mention was made of the immediate cutaneous reaction resulting from each sensitizing injection.

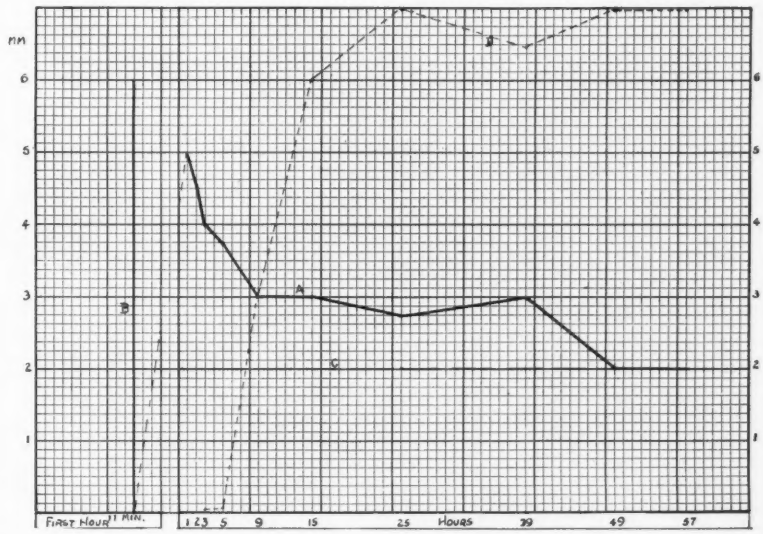

Chart 2.—Antigen tide in W. M. after ingestion of 20 peanuts as traced by the reverse technic, and curve after second feeding of antigen. Serum testing strength 1:4.

A, reverse technic curve.

B, size and time of onset of ingestion (direct technic) wheal.

C, indicating size of cutaneous response to serum.

D, second feeding curve.

A comparison of the wheals produced by the direct and the reverse technics reveals that the latter are smaller and less active than the former. One distinctive feature clinically differentiates the reverse wheal from any other type of experimental wheal. This is a peculiar, deep-seated, nodular induration which persists for a long time at the site of the subsiding reaction. It has been observed to last from eight to fourteen hours after the wheal has begun to decline. The factors responsible for this induration as well as the complete description of the local reaction by the reverse technic are discussed in another communication.[5]

The reverse technic has also been employed to study the absorption of antigen from the respiratory tract. The antigen tides following subcutaneous and other methods of administration have also been investigated in a similar manner.

The reverse technic has provided a means of studying the effects of various medicaments, drugs, and pathologic conditions on the absorption of antigens. These various angles of the question will be reported in future communications.

As in the case of the direct technic, the reverse method has not proved so satisfactory in studies on atopic subjects as it has on normal individuals. This is probably due to the fact that atopic subjects do not accept passive sensitization as well as normal subjects.[6]

One of the many objections to the reverse technic is that its performance demands a high degree of precision which can be acquired only after considerable experience. Other sources of error are many. There are such variables as diminution in the strength of the serum resulting from aging, differences in the quantity of serum introduced with each injection, the unequal reacting power of different skin sites under the same testing conditions, the daily variations in the normal gastrointestinal tract, etc.

In spite of these limitations, however, the reverse technic can furnish valuable information on the degree and rapidity of the absorption and elimination of unaltered antigens, following various methods of administration. It is particularly valuable in that it is a painless and harmless technic which can be used directly on the subject in order to obtain the desired information within a relatively short time.

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DISCUSSION

DR. MILTON B. COHEN.—I think this work is very fine. For experimental purposes, the method has a definite place in the study of the absorption and elimination of antigens. When we worked with this same type of method using inhaled materials, particularly pollen, we did make some of these observations, such as you made in your original curve, Dr. Walzer, but unfortunately I was the test animal in a number of those preliminary experiments and I react to most of those serums nonspecifically. A good many other people did, and I was never able to satisfy myself that I could set up sufficient control of that irritative reaction to determine how far it went or when the specific reaction began. So we left out any reference to the curve you had coming down and devoted ourselves to the curve going up, feeling

we could draw conclusions accurately only upon those in which we obtained complete neutralization of the site from the circulating antigen.

As I read the paper, I saw mention of the fact that you controlled the amount of primary irritability, but I wonder whether in your reply you would give us a little more detail as to how you actually can control it. Obviously you did, in obtaining these curves.

I should like to say, with the exception of that one point about which I have not been able to satisfy myself, that I agree completely with everything that Dr. Walzer has presented here this morning.

DR. A. F. COCA, New York.—I was just afraid we might pass over the experiments of Dr. Donnally on the finding of egg protein in the mother's milk. I had a personal interest in this demonstration because Dr. Donnally allowed me to test the very high-powered serum which he was using and on which his success depended. So, I feel that there is no doubt at all that proteins unaltered can pass not only through the gastrointestinal tract, but actually out again in the secretions of the body.

There is some question in the minds of some of us as to whether we are dealing here, not with an unaltered protein, but with some split product of protein; but I should like to recall some work of Dr. Landsteiner on this question which might have escaped some of us. Dr. Landsteiner has satisfied himself that even the earliest split products of protein have lost their original specificity. Hence the hypothesis just mentioned cannot be used to explain the findings of Dr. Walzer nor those of Dr. Donnally.

DR. ALEXANDER.—There is one point I should like to ask Dr. Walzer or Dr. Ratner, who have worked on this problem. How do these peanut antigens get into the systemic blood? Either they are absorbed through the mouth or esophagus, or they get into the portal blood and go through the liver, or possibly via the lymph of the thoracic duct. As I understand it, in twenty minutes they were in the systemic blood.

DR. COCA.—There is no instance of a restoration of antigenicity in a split product of protein that has lost its specificity through linking it with another protein.

DR. PINESS.—I was wondering, if it lost that, how it can give these reactions.

DR. COCA.—The split products of protein have none of their original specificity; therefore they could not give these specific reactions.

DR. RATNER.—The question Dr. Alexander raised is of tremendous interest to all of us who have been working in this field, that is, the question of the antigens getting through the portal circulation. It seems to me that it is not the channel the unchanged proteins travel, because in a piece of work Mills and Dorst showed, with the use of fibrinogen taken on an empty stomach, that it reached the circulation of the tip of the finger in a minute and one-half in a native state. In our work a guinea pig died within a minute and one-half after drinking 5 c.c. of milk.

In the literature there are reports of reactions that occur upon the inhalation of unchanged proteins usually within two or three minutes. Physiologists and chemists with whom I have discussed this matter of permeability all believe, from their experience with dialyzing membranes, that it is difficult or impossible to obtain a perfect dialyzing membrane. The impression I have is that antigens escape through permeable membranes because of imperfections in the mucous membranes. Nature has attempted to make our membranes perfect enough to prevent us from getting allergy, but not all membranes have this quality and antigens do pass. What we know in allergy is that the membranes do permit the passage of unchanged antigens.

There is one other point, namely, that most workers have failed to find the unchanged proteins in the blood by using the precipitin method. The Prausnitz-Küstner method is far superior. The opportunity for finding it is enhanced by this latter method because, as has been brought out, the antigen remains in the circulation for two or three hours; investigators who have tried to demonstrate it five or six or ten hours later by the precipitin method invariably failed.

DR. A. WALZER.—In answer to Dr. Cohen's question on the serum reaction, I want to say that every subject's skin response to the serum injection without any antigen in the circulation, was carefully noted and measured. It was found that the wheal following the injection of the serum varied somewhat in the different subjects. The average wheal was about 2.75 mm. in diameter, appeared quickly and disappeared rather rapidly, as compared to the immunologic wheal. It was not so indurated nor so active, and did not itch so much.

On the question of the reaction being specific, Dr. Coca has answered that very well. Dr. M. Walzer has shown that fish antigen is in the circulation in two minutes after its ingestion. It is possible that the antigen reaches the blood by way of the portal circulation or thoracic duct, but it is inconceivable how it can do so in so short a time. How it does enter the blood is not understood, but it does pass through somehow.

Dr. Ratner's question that there must be a defect in the mucous membrane to allow the antigen to get through would presuppose that all apparently normal individuals have such a defective membrane, which is not plausible. The absorption of unaltered protein is in all probability a normal physiologic phenomenon, and occurs in every individual.

DR. RATNER.—We have talked to gastroenterologists, and they cannot explain it either. You cannot find it in the blood stream, but you can in the local skin area (Prausnitz-Küstner). My meaning is that you cannot demonstrate it easily by the precipitin test.

STUDIES IN SENSITIZATION*†

Influence of Occupation on Sensitization in Man as Determined in a Study of Thirty-Two Bakers

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IN SPITE of the recent advances in the study of the mechanism and the clinical manifestations of allergy, little progress has been made in the understanding of the allergic individual, the host. Aside from heredity as the determining factor in the establishment of the hypersensitive state in man, from clinical observations alone there would seem to be other factors which tend to influence this process to a greater or lesser extent. Thus, it is generally agreed that the frequency and the quantity of exposure to a given allergen may mark the time of onset of sensitization, while the "receptive state" or vulnerability of the shock organ may determine the type of sensitization. Moreover, not all persons with a hereditary background of allergy become clinically hypersensitive, while instances of sensitization in the so-called normal persons in the absence of a positive family history of allergy, are not uncommon. The question then arises as to which of the several factors involved exerts a greater influence on human sensitization: the constitutional make-up of the individual, the quantity and frequency of exposure to the allergenic substances, or the vulnerability of the shock organ? Is there, after all, a normal individual who resists sensitization under all possible conditions, or is the difference between normal and susceptible only a matter of degree, as pointed out by Rackemann?[1]

An opportunity to study these questions presented itself through the courtesy of the Boston Branch of the Continental Baking Company, which granted us permission to investigate the incidence of sensitization to flour in a group of 32 bakers.

In the bakery, the workers are exposed to four types of flour, in order of their importance: wheat, rye, corn, and barley. Not all men, however, are exposed to the same concentration of flour dust, since the industry is divided into several departments. The flour dumper, for example, almost bathes in a thick cloud of dust; while the packer,

*From the Anaphylactic Clinics of the Beth Israel Hospital and Massachusetts General Hospital.
†Read at the combined meeting of the Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., June 10, 1935.

who wraps the baked loaf with cellophane, is exposed to flour dust hardly at all. Between these two extremes, there are the departments of flour mixing, dough making, form making (make-up room), moulding, baking, and racking.

The general sanitary conditions of the Boston Branch of the Continental Baking Company are ideal. Cleanliness is insisted on, and every effort is made to maintain it. The rooms are spacious, light, and well ventilated. "Flour dusting" as a necessary part of the process of baking is controlled as much as possible by clever mechanisms which drop only the proper quantity of dry flour on the lump of dough in the moulding machines. In spite of the general cleanliness and effort to control the dust, the fact is, however, that the visitor is aware of a thin veil of dust which permeates the entire building, even to the corridors. Therefore, no matter in what capacity one is employed, he cannot escape the inhalation of flour.

The study was divided into two parts: case history and skin tests.

Under case history, the following points were considered: (1) length of time spent in the baking industry; (2) type of work engaged in by the individual worker; (3) family history of allergy; (4) past history of allergy; (5) presenting symptoms of allergy, if any.

ANALYSIS OF DATA

The length of time engaged in baking industry ranged from one year or under in five cases, to twenty-four years in one case. Only one baker, Case 5, was clinically sensitive to flour. Although he had been in the baking industry for twenty-two years, his asthma dates back only six years. The other 31 bakers experienced no ill effects from the inhalation of flour.

The type of work engaged in by the individual worker was considered in relation to the influence of the frequency and quantity of exposure to flour, to sensitization. It was found, however, that the workers were shifted from time to time to different positions, in a way of promotion, and that in this way most of the men at one time or another were exposed to all possible concentrations of flour dust. The flour dumper (Case 2) was a striking exception, for this man had remained on the same job for eight years. Unquestionably, flour dumping, from the sensitization point of view, seems most hazardous, and yet the man on this job was free from any clinical evidence of sensitization to flour. He did have occasional sneezing spells, which, however, were not related to his work. In Case 5, the baker has had asthma for six years, and was engaged at the time of this investigation in dough mixing, a process accomplished chiefly by a machine, and yet he had to wear a mask for comfort.

The family history was either unknown or negative in all but one baker (Case 2) who gave a history of eczema on his paternal side.

The past history was negative for allergy in all cases.

Presenting Symptoms of Allergy.—(a) *Respiratory.* In Case 4 the man has had mild hay fever in June, and in Case 12 the baker has been subject to grass hay fever for several years. Perennial asthma of six years' duration occurred in one baker, Case 5, who, however, has always been worse at work and has worn a mask. Morning cough with occasional wheeze occurred in one, Case 22, but his trouble was not related to his work.

(b) *Skin.* In Case 5, the baker has had asthma, and is also subject to urticaria.

In summary we may say that in the 32 cases studied, a family history of allergy occurred once, while frank manifestations of allergy occurred in two (one man had asthma and also urticaria, while another had hay fever). A third (Case 6) may have had mild hay fever in June.

Skin tests were performed intradermally with extracts of wheat, rye, barley, and corn, freshly prepared with Coca's extracting fluid. After filtering the extracts through Seitz filters, their nitrogen contents were determined and dilutions were prepared representing 0.1, 0.01, and 0.001 milligrams of nitrogen per c.c.

In order to establish the potency of the extracts, we tested intradermally two known wheat sensitive patients, nineteen noncereal sensitive allergic individuals, and three normal persons. The latter and six of the allergic control individuals failed to react to any of the concentrations used. The extracts were nonirritating. The 13 other allergic individuals and two known wheat sensitive patients reacted to all cereals and practically to all dilutions. The extracts were potent.

In the 32 bakers, positive reactions to one or more flour extracts occurred in 15, or about 47 per cent. Barley was positive 13 times, corn ten times, rye 8 times, and wheat 6 times. Ragweed extract in 1:1,000 dilution, which was used as a control, was positive 8 times, although none of the reactors gave a history of ragweed hay fever. To correlate the incidence of positive skin reactions to flour with the duration of exposure, the 32 bakers were divided into two arbitrary groups, according to their years of employment. One group comprised 26 men who have spent one to twelve years in the industry; the other consisted of 6 men who have been engaged in this work from thirteen to twenty-four years. In the former group, 11 of the 26, or 42 per cent, gave positive reactions to one or more cereals; while in the latter, 4 of the 6, or 66 per cent, gave positive reactions.

An additional part of the investigation consisted of patch testing this group of workers in order to determine the incidence of skin or

contact sensitivity to the various ingredients used in the baking industry. That such sensitivity may occur in eczematous bakers as contrasted with normal controls was pointed out by Zitzke[2] in 1932. In the same year Kennedy[3] and in 1930 Wise[4] described two additional cases of contact sensitivity to lactic acid and dough, respectively, in eczematous bakers. On this basis, dough and lactic acid, in a 40 per cent dilution (the latter nonirritating to normal persons), were used in patch testing the group under investigation. These tests were read at the end of ninety-six hours.

The dough failed to give any positive reactions. This may be explained by the fact that we used fresh instead of fermented dough, the former being free from lactic acid. Patch tests with lactic acid alone, however, were positive in 14 of 32 bakers, or 44 per cent. Of these, 9 were constantly handling dough, while the other 5 were employed in other parts of the baking industry. This may indicate that where contact with fermented dough was more intimate, positive patch reactions to lactic acid were more frequent. Yet, that this was not true in every instance was noted from two employees who had a persistent dermatitis of the right hand. One of them, the superintendent of the establishment, gave a positive lactic acid patch test, while the other, a dough mixer, was patch test negative.

COMMENT

In this investigation no attempt has been made to emphasize the importance of occupational or environmental allergy. In fact, from the observations of Cooke,[5] Van Leeuwen,[6] Ratner,[7] Peshkin[8] and numerous other contributors, it has been well established that the acquisition of all hypersensitiveness in man is related to the individual's environment, food, or occupation. Rather are we concerned here with an evaluation of the factors which tend to disrupt the balance of the scales on which the host and the allergenic substances are normally in a state of equilibrium.

We are cognizant of the fact that any conclusions drawn from this investigation must be considered as tentative, since the number of cases studied is small. Yet it may be reasonable to assume that this small group of 32 bakers represents a cross-section of the employees in the baking industry at large.

The factor of heredity did not uphold its traditional rôle of importance in this group. In Case 5, for example, the baker suffered from asthma; and in Cases 4 and 12 they were subjected to seasonal hay fever; all three gave a negative family history for allergy. On the other hand, in Case 2, the baker who had allergy on his paternal side, and thus might have been endowed with a capacity for sensitization, was clinically non-sensitive.

TABLE I

SKIN REACTIONS IN 32 BAKERS EXPOSED TO FLOUR

CASE NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Age	49	49	35	55	36	34	31	26	24	30	34	40	20	32	29	22	38	54	19	57	38	33	21	48	20	19	64	21	39	29	33	53
Years a baker	4	8	7	6	22	6	2	6	5	2	4	20	2	10	13	2	6	9	1	7	8	5	1	24	1	8m	3	1	20	11	2	13
Symptoms		S		HF	A				C			HF										W						D				
Intradermal Tests																																
Barley	0	+	0	+	+	+	0	+	+	0	0	+	0	+	+	0	0	0	+	0	0	+	0	+	0	+	0	0	0	0	0	0
Corn	0	0	0	+	+	0	0	+	0	+	+	+	0	+	+	0	0	0	0	0	0	+	0	+	0	0	0	0	0	0	0	0
Rye	0	+	0	+	+	0	0	+	0	0	0	+	0	+	+	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0
Wheat	0	0	0	0	+	+	0	+	0	0	0	+	0	0	+	0	0	0	0	0	0	0	0	+	0	+	0	0	0	0	0	0
Ragweed	0	0	0	+	+	+	0	+	0	0	0	0	0	0	+	+	0	0	0	0	0	+	0	+	0	0	0	0	0	0	0	0
Patch Tests																																
Lactic acid	0	+	0	+	+	0	+	0	0	0	+	0	+	0	0	+	+	0	0	0	0	0	+	0	+	+	+	0	0	0	0	
Dough	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

S = Sneezing.
HF = Hay fever.
A = Asthma.
C = Cough.
W = Wheeze.
D = Dermatitis.

Shock organ vulnerability was evident in Cases 4 and 12, by virtue of their seasonal hay fever, and yet these two workers failed to manifest any clinical sensitivity to flour. Likewise, in Case 22, the baker who has had a morning cough and wheeze for many years had no ill effects from contact with flour. Evidently, the possession of a vulnerable shock organ does not necessarily dispose one to multiple sensitivities of clinical importance. A corollary to this is to be found in the pollen sensitive patients, who in the majority of instances have but one type of hay fever, such as ragweed, to the exclusion of other types of hay fever.

The influence of the quantity of exposure to a given allergen on the establishment of clinical hypersensitiveness is interesting. As previously stated, all the bakers have been exposed to varying concentrations of flour dust in the course of their careers. But most conspicuous is Case 2, the flour dumper, who in spite of an uninterrupted exposure to a high concentration of flour dust for a period of eight years has failed to become clinically hypersensitive. Yet this man's father and father's brother had eczema. Judging from this case alone one may assume that, after all, there is a so-called normal person who resists sensitization under the most hazardous conditions. Likewise the duration of exposure to flour dust did not bear any manifest influence on the establishment of clinical sensitization in this group. Thus in Case 5: the baker who had flour asthma has worked in the industry for twenty-two years; while the bakers in Cases 4 and 12, subject to seasonal hay fever, but who failed to become flour sensitive, have been in the industry for six and twenty years, respectively. The subject in Case 24, who was free from any symptoms, has been a baker for twenty-four years.

The other phase of this study, the skin tests, lends additional interest. That 15 of 32, or 47 per cent, in this group were skin sensitive to flour, whereas only one individual was clinically sensitive, is significant. It certainly indicates a preponderance of skin sensitivity over clinical sensitivity, and this is in accord with our other observations on a number of so-called normal individuals in whom the incidence of positive skin reactions is high. Similar results were noted in the study of our control group, in which 13 of 19 noncereal sensitive allergic individuals gave positive reactions to all cereals.

Another interesting fact is that most of the bakers who were skin sensitive at all, reacted to all of the four grain extracts. Indeed, wheat was the least frequent reactor. This latter observation has a bearing on our attempts to desensitize bakers to wheat alone in the face of existing additional sensitivities to barley, corn, and rye, all of which are used in the baking industry and could well be additional exciting factors.

The data obtained in this study tend to shake certain of the fundamental concepts of clinical allergy, particularly those that pertain to the accepted influences of heredity and shock organ vulnerability on the establishment of clinical hypersensitiveness. Several postulates, however, may be drawn tentatively in the following conclusions.

1. Given a sufficient exposure to a substance of known allergenic potency, the establishment of clinical hypersensitiveness is not determined wholly by heredity or by the frequency and degree of exposure, or by the vulnerability of the shock organ.

2. Given all known factors favoring sensitization as enumerated above, there still remains an unknown biologic factor, an activator which permits the successful participation of the known factors in the accomplishment of the hypersensitive state.

3. To become skin sensitive is a common property of mankind; while the capacity to express the sensitivity clinically is the property of those in whom the intrinsic factor, the activator, is operative.

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DISCUSSION

DR. SAMUEL M. FEINBERG, Chicago.—May I ask whether in testing for all these ingredients Dr. Rackemann did not consider the use of yeast?

DR. HARKAVY.—Although this paper is rather brief, it is very valuable. Its importance lies in the fact that it suggests that repeated exposure to an antigen may give rise to positive skin reactions. This may indicate a state of sensitization not necessarily associated with local symptoms. In other words, a positive skin reaction cannot be interpreted as diagnostic of a disease process. It must simply be regarded as indicating skin sensitiveness and that is all. We still have to go back to the well-established principle, namely, that before we can interpret a positive skin reaction as etiologically significant, we must be able to correlate it with the clinical manifestations.

It is interesting to note that a certain percentage of the authors' subjects reacted to ragweed without symptoms. It will be of value to find out whether those who gave skin reactions to wheat also reacted to timothy, on the basis of the interrelationship existing between the cereals and the grasses. Dr. Vaughan has pointed out this relationship, and it may be important in treatment of certain types of cases.

In testing almost 400 normal individuals with ragweed, timothy, horse dander, and tobacco, we found that between 27 to 34 per cent

reacted to various combinations of ragweed, timothy, horse dander, and tobacco. Of these, 10 to 15 per cent actually had active symptoms of hypersensitiveness due to these allergens. Twenty-five per cent had personal or family history of allergy.

This again emphasizes that skin sensitiveness to true antigens, provided we do not deal with irritable skins, may be the result of inherited traits (constitutional allergy) unless they are due to acquired sensitivity as suggested by the observations of Dr. Colmes. Focal symptoms, as Coca and others have pointed out, postulate the existence of a shock organ.

DR. WILLIAM W. DUKE, Kansas City.—I once studied the case of a flour miller who had asthma. Our routine tests, both clinical and skin tests, were negative. I finally obtained positive tests by mixing chlorine with the wheat extracts. In the mill in which he worked chlorine was used for bleaching the flour. He apparently reacted to a mixture of chlorine and wheat.

DR. RACKEMANN.—The point of these observations is that the skin test and the symptoms do not go together. Apparently, it is easy for the individual to develop positive skin reactions, but it is difficult for him to develop clinical symptoms. Dr. Colmes has brought out that the two atopic individuals in the series were among those who did not develop any sensitiveness to wheat. As a preliminary thought, we have considered that there might be some additional factor, some "activator" in the make-up of persons who develop symptoms from exposure to dust in their occupation.

RAGWEED (CONTACT) DERMATITIS PRODUCED EXPERIMENTALLY IN THE GUINEA PIG

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THE importance of members of the ragweed (Ambrosia) group as excitants in the production of recurring seasonal dermatitis has been discussed recently by one of us (Brunsting) and Anderson.[6] We confirmed the conclusions of Bengtsson,[2] of Brown, Milford, and Coca,[5] and of Pascher and Sulzberger[7] to the effect that this type of acquired contact sensitivity is due to the fat soluble fraction of the plant in contrast to that water soluble portion which is known to be the atopic excitant.

Experimental studies on the production of contact dermatitis in animals by vegetable irritants have been reported by Bloch and Steiner-Wourlisch,[4] and by Simon, Simon, Rackemann, and Dienes,[8] who sensitized guinea pigs to primrose and ivy, respectively. There is an earlier report by von Adelung[1] on the sensitization of rabbits to Rhus toxin and leaves. In this paper we present our observation on the development of contact sensitivity in guinea pigs to ragweed, a procedure which was planned as a preliminary to an attempt at desensitization. In order to approach most nearly to the mechanics of natural contact in man, the oily irritant of ragweed in relatively weak dilution was applied repeatedly to normal, apparently unbroken skin.

EXPERIMENTAL METHOD

Guinea pigs of medium size, and a preponderant number with a light skin, were chosen. A portion of skin on the upper part of the back, approximately 4 cm. by 6 cm. in size, was epilated by plucking. Twenty-four hours later, the site being free from signs of erythema or excoriation, daily painting of certain of the animals was begun with a 5 per cent ether dilution of a concentrated fat-solvent fraction of short ragweed plant and pollen oil; other animals were painted with a 5 per cent olive oil dilution of mixed, short, and giant ragweed pollen oil. Fine camel's hair brushes were used, and a space approximately 2 cm. in diameter was painted, the faint green color produced by the slight amount of chlorophyl in the oil being sufficient to delineate the site. Control animals were similarly prepared and painted daily with olive oil or ether. In any given case painting was discontinued at the first signs of definite irritation of the skin.

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After a sufficient interval following the appearance of dermatitis at the primary site, test sites were prepared adjacent to this area of dermatitis and on the opposite shoulder. To each of these sites one minim of a 1.25 per cent ether dilution of the original extract was applied with a dropper. Similar application of other materials was made,* including the extract of burweed marsh elder of identical preparation and concentration, as well as various other unrelated substances in common use for patch testing. Punch biopsies of affected primary sites were taken, and in sensitized animals blood was drawn for passive transfer.

Fig. 1.

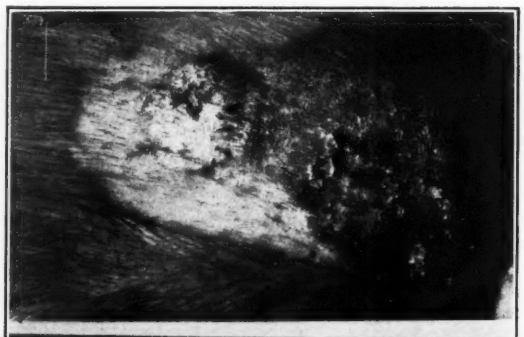

Fig. 2.

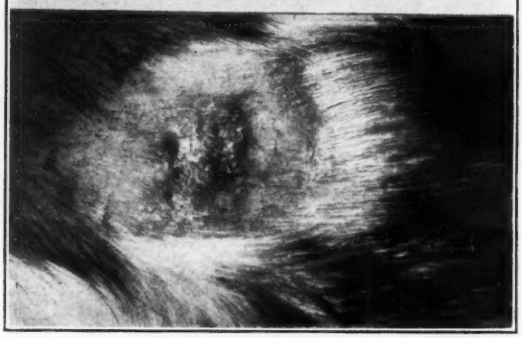

Fig. 1.—At the right is the primary site six days after discontinuing daily painting. At the left is a test site seventy-two hours after the application of one minim of a 1.25 per cent ether dilution of the ragweed extract.

Fig. 2.—The opposite shoulder seventy-two hours after application of the same testing dilution.

Twenty guinea pigs were prepared in this way in the spring of 1934. Of this group, one was painted daily with ether alone and one with olive oil alone without the development of the least sign of irritation throughout the entire period of painting. Four were painted daily with the olive oil dilution of short ragweed pollen extract. These guinea pigs had no more than transient erythema at any time. Of the remaining fourteen guinea pigs painted with the ether extract, three had a persistent erythema beginning on the tenth to the thirteenth

*Concentrated oily extracts of ragweed and burweed marsh elder were furnished through the courtesy of Marjorie B. Moore, Ph.D., Chicago.

day. This erythema was localized at the site of the paintings. In the next four days the plaque became successively more deeply erythematous, swollen, weeping, and fissured, and it finally presented a crusted appearance similar to the picture of eczema in man. Specimens for biopsy at this time had the typical microscopic characteristics of eczema. The crusting and erythema gradually subsided over a period of five or six days. The application of one minim of 1.25 per cent ether dilution of ragweed extract to nearby and remote sites of the skin caused a series of changes identical to those just described in the sensitized guinea pigs on repeated trials up to three months following sensitization (Fig. 1, right and left, and Fig. 2). Similar application to the entire remaining number did not result in erythema. Painting of the remaining eleven animals was continued for a further period of two weeks without evidence of erythema or dermatitis becoming apparent at the primary site.

The sensitized guinea pigs were tested to an ether dilution of burweed marsh elder extract but gave no evidence of erythema. Similar tests were done with solutions of the following materials: quinine hydrochloride, bichloride of mercury, potassium arsenite, primrose, orris root, and turpentine. Slight transient erythema was noticed in a few cases, but no reaction sufficiently distinct to be considered positive was obtained.

In no case was passive transfer of blood by Prausnitz-Küstner technic from sensitized to nonsensitized guinea pigs successful.

SUMMARY AND CONCLUSIONS

Experimental contact dermatitis to ragweed was produced successfully in three of fourteen guinea pigs by repeated painting of the apparently normal, unabraded plucked skin with a relatively weak solution of the specific vegetable oil in ether. In the sensitized animals it was observed that:

1. Erythema first appeared at the site of primary reaction after an incubation period of ten to thirteen days.

2. The mature primary reaction was typically eczematous in gross and microscopic appearance.

3. Hypersensitivity of the skin was apparent at sites far removed from the primary reaction.

4. Applications of the original sensitizing solution of short ragweed in weak dilution gave positive test reactions.

5. Application of extract of the related burweed marsh elder gave no reaction.

6. Applications of solutions of other common cutaneous irritants gave no reactions.

7. Passive transfer by Prausnitz-Küstner technic was unsuccessful. In none of the unsensitized animals were positive test reactions obtained.

These observations are in agreement with the concept of contact sensitivity as defined by Bloch.

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PERMANENT RESULTS FOLLOWING TREATMENT FOR LATE HAY FEVER*

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AND
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HAY FEVER is a disease of long duration, the onset of which is gradual, becoming worse each season until a certain peak is reached, and then gradually subsiding. We all know of persons, usually relatives of our patients, who have outgrown their hay fever. No figures are available on the number of years the condition may last. The question which interests all of us is, "Does the injection of pollen extract shorten the natural course?" Scheppergrell, Vander Veer, Thommen, and others have discussed the question, but by far the most enthusiastic writer has been Walker.[1] In his most recent paper last year he reports 26 per cent of "cures." In that paper he stresses the importance of many years of treatment, the cures increasing from 8 per cent of those treated only one year up to 65 per cent of those treated five years. Other writers estimate between 6 per cent and 15 per cent cures.

In the present study we interested ourselves not only in those who were entirely relieved or "cured," but also in those who were definitely but incompletely relieved. Since the ragweed sufferers are resistent to treatment and since ragweed pollen occurs in much more uniform concentration than do the other pollens, we restricted our study to the late summer type of hay fever. A questionnaire was sent to all persons who had taken at least ten doses of pollen extract and in whom at least two seasons had elapsed since treatment was stopped.

Approximately one-half of those to whom a questionnaire was sent were included in the study. Some could not be traced. Others had taken injections from other physicians. This study is based on the answers to the simple question, "If you are still suffering from hay fever, do you consider it as severe as it was before taking specific treatment?" The New York and Philadelphia groups were studied independently; and, when the results were compared, we were struck by the difference obtained. For this reason the two groups are listed separately in Table I.

The pollen solutions, while made in different laboratories, were supposed to be the same. The same ideas of dosage and testing were

*Presented at the combined meeting of the Society for the Study of Asthma and Allied Conditions and the Association for the Study of Allergy, Atlantic City, N. J., June 10, 1935.

used in both groups. Furthermore, the results in the seasons treated were about the same for both groups. There were 20 per cent unsatisfactory results in both, and excellent results were obtained in 24 per cent of the New York group to 20 per cent of the Philadelphia group.

TABLE I

PERMANENT RESULTS FOLLOWING TREATMENT FOR LATE HAY FEVER

	COMBINED SERIES	PATIENTS	
A	"Cured"	31	20%
B	Greatly relieved	53	33%
C	Decidedly relieved	21	13%
D	Hay fever as severe as before treatment	54	34%
	Total	159	100%

	NEW YORK SERIES	PATIENTS	
A		22	23%
B		39	42%
C		9	10%
D		24	25%
	Total	94	100%

	PHILADELPHIA SERIES	PATIENTS	
A		9	14%
B		14	21%
C		12	19%
D		30	46%
	Total	65	100%

We believe that the difference shown between the New York and the Philadelphia groups is due to the greater amount of treatment given to the former and to the difference in pollen exposure in the two cities. We further believe that these two factors will determine the permanent results which may be expected by other workers in different parts of the country.

TABLE II

AVERAGE NUMBER OF YEARS TREATED

		NEW YORK SERIES	PHILADELPHIA SERIES
A	"Cured"	6.2	3.6
B	Greatly relieved	5.3	2.9
C	Decidedly relieved	2.4	2.2
D	Hay fever as severe as before treatment	3.8*	2.2

*Eliminating three cases treated 14, 11, and 9 years, the average years treated was only 2.4.

The importance of many years' treatment has already been emphasized by Walker. Our data are given in Table II. Here it should be noted that in the C and D groups (those who had least permanent benefit from their treatment) the years of treatment were approximately the same in the two groups, 2.2 and 2.4 years. Discounting the importance of this factor, is the fact that those who obtained the greatest relief are more likely to repeat the treatment. The importance of successful seasonal treatment is emphasized in Table III.

Little permanent relief is to be expected from any treatment which fails to give relief during the season for which it is given. While the second and subsequent years' treatment are likely to be better than the first, we cannot share all of Walker's optimism on this point. Unless we can make some radical change in our treatment, a failure is likely to repeat itself.

TABLE III

PERMANENT RESULTS COMPARED TO SEASONAL RESULTS
(BOTH SERIES)

	EXCELLENT (+++) SEASONAL		SATISFACTORY (++) SEASONAL		LITTLE OR NO RELIEF FROM SEASONAL TREATMENT	
A "Cured"	20	53%	10	12%	1	3%
B Greatly relieved	13	34%	33	38%	4	12½%
C Decidedly relieved	3	8%	14	16%	4	12½%
D Hay fever as severe as before treatment	2	5%	29	34%	23	72%
	38	100%	86	100%	32	100%

The pollen concentration in the atmosphere is the greatest factor in deciding the degree of success of treatment. We who work on the Atlantic seaboard all remember the trouble we had in 1931 when the pollen counts were almost twice as high as the average. Since the permanent results depend on the seasonal results, those working in areas in which large counts are the rule cannot expect the results which are obtained in Boston and New York. Durham,[2] working over a five-year period from 1925 to 1929, rates Boston at 50, New York at 101, and Philadelphia at 165. These can be compared with Indianapolis, in the heart of the corn belt, which had a rating of 826. Black of Dallas reports improvement, but no complete cures with a rating of 299.

The recurrences are worthy of note and of further study. In the combined series, out of a total of 105 persons receiving permanent results, 14 have recurred; 3 of the +++ group, 9 of the ++ group, and 2 of the + group. These all occurred the third or fourth year after treatment was stopped. We can state no percentages because, in many of those reported, four years have not yet elapsed since treatment was discontinued.

Another small group reported that each season became milder after treatment was stopped, and two of these reported complete freedom on the third and fourth year without treatment.

Other slight differences were observed, as follows: Women fared slightly better than men. Those under thirty were better than those over thirty years. Those with more strongly positive skin reactions; those with stronger eye reactions; those whose hay fever was of

shorter duration; and those who had tolerated larger subcutaneous injections were likewise more favorable. These differences, however, were so slight that they might easily be reversed in a larger series.

The study has not shown any criterion by which we can predict who will and who will not obtain permanent relief. A small percentage of persons are cured by one season's treatment, while others after fourteen years still suffer as severely as ever. We have one remarkable instance of "cure" from insignificant dosage. This woman came for phylactic treatment in the middle of the 1924 season and received only four small doses. She has had no hay fever since. It would seem that there is more than one immunologic mechanism involved and that a number of different types or diseases are included in what we now recognize as hay fever.

We have no adequate figures on the disappearance of the skin reaction in those who are cured. Some of these have been retested, and it is our impression that there has been little change. We have, of course, seen the skin reaction disappear, but we regard this as the exception rather than the rule.

CONCLUSIONS

Permanent relief from hay fever can be expected from specific pollen injections in well over 50 per cent of those treated.

This percentage is higher in those whose treatment covers a number of years, the best results occurring in those treated from five to eight years.

The more successful the seasonal treatment, the more likely are the results to be permanent.

The higher the pollen content of the atmosphere, the less likely is the result to be permanent.

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DISCUSSION

DR. PINESS, Los Angeles.—This rather interesting report makes me think of previous reports published, among them being one by Dr. Vander Veer and others. I am impressed with the fact that in the cases reported to date the patients who have been under treatment over a long period of time do not show results that are more striking than those reported by other workers as mentioned above.

I take issue with Dr. Vander Veer, a friendly issue as it were, against using the term "cured." I think it would be better to say "free." If we used the same classification, we would get more reliable information. One must interpret the reports such as the one we heard today from purely a personal equation.

We are all prone to think that our own work is good and that our reports should be in proportion to what we think is being accomplished. We all wish, however, to be honest in presenting these reports, and I think this one demonstrates rather conclusively that such results are perhaps a little better but on the whole only comparable with the results that all of us have been getting during the past twenty years.

I do not believe that dosage determines the result in a given case and that dosage and reactions do not go hand in hand. Dr. Clarke mentioned that in one particular case minimum dosage gave excellent results. I find in my own experience that we cannot carry on treatment with a stereotyped plan of dosage and that the poorest results are obtained in cases referred back to physicians in the rural communities who are dependent upon a stereotyped schedule of treatment. I feel that we must place less dependence upon our dosage and more upon the individual case as we meet it.

Dr. B. Gelfand Efron, New Orleans.—Some one has said that you could prove anything you want to with statistics. After reading the statistics on hay fever results, I cannot get very much out of them because none of the statistics contain a control series. Sometimes when we ask a patient how he is doing, and find he is having no hay fever, much to our chagrin he will tell us that three or four of his hay fever friends are not having any trouble either, although they are taking no treatment. Before we can place any reliance whatsoever on any group of statistics of treated cases, we should have a similar series of patients known to have hay fever and who have not had specific treatment.

Then, on the question of what constitutes a satisfactory result, a patient starts treatment in middle of the hay fever season, if he then has less hay fever than he had previously, he considers himself relieved; however, when a patient has been treated for two years and still has a small amount of hay fever, he may become dissatisfied. If our results are based on what our patients tell us, the results will not be accurate. Until we find some method of measurement, counting either the number of sneezes or the number of handkerchiefs used, we cannot place too much or too great reliance on any group of statistics.

Dr. J. A. Clarke.—I do not know whether we are being attacked or not. No statistics are any better than the man who gives them. As for the use of the word "cured," it is handy, being of only one syllable; but when you see the paper published you will note that the word "cured" is in quotation marks.

As for the control series, it has been our uniform practice, on the first of October, to send all these people a questionnaire, asking them to place themselves in one of four groups: hay fever—absent; greatly relieved; slightly relieved; or no effect at all. It is on the answers to these questionnaires obtained at the end of the season that we base our statistics. It is as accurate as anything we could get together. We have tried our best to be honest.

One criticism I do feel is necessary. We have neglected to state in our series the total pollen count for the year, and this might make considerable difference. We have run the pollen counts for only six or seven years, and this paper covers more than fifteen years.

SURGICAL ANESTHESIA DELIBERATELY INDUCED BY ETHER FOR THE SEMIPERMANENT RELIEF OF CHRONIC INTRACTABLE BRONCHIAL ASTHMA*

PRELIMINARY REPORT

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MODERATELY severe cases of uncomplicated bronchial asthma of specific pollen etiology, even those with an epinephrine requirement of as great as from six to eight doses in twenty-four hours, can almost invariably secure symptom freedom, or at least a marked degree of relief, in a very few days in an air-filtered, pollen-free hospital room under continuous rest and proper attention to required dietary and other specific and nonspecific antigenic details. The failure to secure such anticipated good result, with the successful relief measure subsequently instituted in Case 1, is the occasion for this report. Thus far, my experience with this line of therapy has been limited to cases primarily of pollen etiology, with essentially negative surgical nasal pathologic conditions and without other complications that might act as contraindications to general anesthesia.

CASE REPORTS

CASE 1.—Mrs. X, aged thirty-nine years, was first seen Jan. 12, 1934, in consultation with Lt. Col. S. W. French and Major George C. Beach on account of bronchial asthma for the previous month with a daily epinephrine requirement of from six to eight doses. Skin tests had been positive to pollens consistent with a past history of several years of minor seasonal annoyance. The patient was not very ill or uncomfortable, and physical examination showed nothing beyond the usual chest findings of this type of case. No cause could be found for the failure of relief following the close of the etiologic fall pollen season. A ten-day stay in an air-filtered, pollen-free hospital room (Nix Hospital, San Antonio), with usual dietary and specific and nonspecific antigenic precautions, resulted in no improvement.

Inasmuch as apparently definite radiographic evidences of nasal accessory sinus abnormality were found, I naturally concurred in the nasopharyngeal consultant's advice of an antral puncture and washing, and after the reported finding of some pus, a bilateral antral window operation. On January 29, two days later, this was performed

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by Lt. Col. Royal Reynolds. The operation had to be concluded under general anesthesia after the patient's nervousness and restlessness prevented more than its mere inception under the usual local anesthetic. No pus or pathologic condition, beyond thickened mucosa, was found.

However, immediate relief of the asthma followed. Total withdrawal of the epinephrine became possible at once; the chest cleared completely of signs of bronchitis, subjective and objective, for the first time in six weeks. Preseasonal pollen desensitization was advised, but proved unsuccessful, and in September, seven months after the relief in the early spring, asthma promptly returned at the onset of the San Antonio fall carelessweed, grass, and ragweed pollen season. Probably on account of very limited previous rainfall, there was practically no summer pollination of grass and carelessweed in San Antonio in 1934, which could easily account for no earlier relapse of the patient. The former usual daily epinephrine ration was again required; and this state of affairs continued through the entire pollen season, which lasted in 1934 until about December 1. Nasal examinations showed the antral windows open and no infection.

When seen by me again on November 15, this patient was once more placed in an antigen-free, air-filtered hospital room (Nix Hospital), and was given another ten-day bed rest. While the degree of the asthma could never be classified as other than that of moderate severity, and complete temporary relief was invariably secured by epinephrine administration, it was not possible to secure the slightest reduction in the number or size of the usual daily six to eight doses required. No testing, specific or nonspecific treatment, or other drug medication of any kind was given during this period to avoid interfering with results.

In the absence of all infection, the control of current atmospheric pollen during the observation period, and the failure to secure the slightest improvement under rest and the removal of all discoverable antigens in a nearly perfect hospital environment, this patient seemed an ideal case for some form of sedative or nonspecific therapy. Recalling the good results following the nasal operation of the previous spring when no significant pathologic condition had been found or corrected, I wondered whether such relief was not due actually to the general anesthesia and not to the coincidental surgical procedure. This seemed reasonably plausible in view of the fact that confirming Maytum's report,[1] I had in several cases each year employed rectal ether and olive oil anesthesia with most satisfactory immediate results, but always, however, only as a desperate life-saving measure for the relief of the most severe type of status asthmaticus, where epinephrine and other antispasmodics had completely failed for the time being, and where a fatal termination seemed imminent.

I had never previously deliberately employed or heard of the employment of this line of treatment in a case of only moderate severity, completely clear of asthma at the time of its administration, and given deliberately with the idea of breaking the paroxysmal "habit," and with the hope of securing at least an appreciable period of symptom freedom. Accordingly, on November 25 a trial rectal ether and olive oil anesthesia was induced by introducing a total of seven ounces of equal parts in the mixture over a period of twenty minutes. The result was a light anesthesia of several hours' duration. Within twenty-four hours, the epinephrine requirement dropped to one or two three minim doses in twenty-four hours. On November 29, four days later, against advice, the patient left the hospital and returned home, the asthmatic bronchitis being still obvious. Light home exertion was resumed with the result that within a week the epinephrine requirement gradually rose again to the usual six to eight, five to six minim, daily doses.

In view of the appreciable benefit from the light rectal ether anesthesia, the patient, her surgeon husband, and myself felt that a trial of a deeper general inhalation anesthesia offered at least a possibility of producing more complete and more lasting benefit which was worth trying. Consequently, on December 15 general surgical anesthesia was induced by nitrous oxide and oxygen, and maintained by ether inhalations in the usual manner for ten minutes, 240 c.c. of ether being used, and followed by no oxygen or carbon dioxide (Station Hospital, Fort Sam Houston). The result was two doses of epinephrine during the hospital stay of twenty-four hours subsequent to the anesthesia, and none was required thereafter.

Eleven days after the last anesthesia experience, the patient was retested to her etiologic pollen factors, and there was absolutely no change in the original strongly positive dermal reactions.

During preseasonal specific desensitization, about one month later, the former asthma returned, and after a week of increasing discomfort, the patient on February 22, 1935, submitted to another ether inhalation anesthesia of twenty minutes' duration at the Station Hospital, but for the following six days there was no improvement (probably on account of daily severe dust storms). The only difference found between the last unsuccessful and the previous successful anesthesias was the total absence of vomiting following the unsuccessful anesthesia. Accordingly, the patient, on March 4, induced considerable vomiting by the use of syrup of ipecac. There was immediate temporary improvement, and epinephrine withdrawal was accomplished March 23, and up to this writing (May 22), there has been no occasion for its resumption.

CASE 2.—Mrs. L., aged forty-two years, first seen Dec. 30, 1934, gave a history of the inception of asthma in Illinois in August, 1934. Skin tests were negative in Illinois and in my office, although the case was undoubtedly one of primary pollen etiology, according to subsequent history. There was a daily epinephrine requirement every three to four hours. Nasal examination was negative. Coseasonal pollen treatment and the usual antigenic precautionary measures were unsuccessful. Her financial condition precluded a prolonged stay in an antigen-free hospital room. On Jan. 25, 1935, gas-induced, surgical ether inhalation anesthesia for ten minutes resulted in a reduction of the epinephrine requirement of 50 per cent. Three weeks later, gas-induced surgical ether anesthesia for twenty minutes resulted in a further reduction of the epinephrine requirement to from one to two or three minim doses in twenty-four hours for three weeks. Then the epinephrine requirement rose with the onset of the tree pollination season to three or four minim doses in twenty-four hours. The patient then returned to Illinois. She reported May 13, 1935, an average epinephrine requirement of three or four minims twice a week.

CASE 3.—Mrs. N., aged twenty-seven years, first seen Dec. 26, 1934, suffered severely from bronchial asthma caused by ragweed and mountain cedar. Coseasonal pollen treatment was unsuccessful. She required seven doses of epinephrine daily, and on one occasion she required epinephrine intravenously as a life-saving measure. The epinephrine requirement continued unchanged for one month following the close of the cedar season. No further significant antigens could be discovered. Nasal examination was negative. Her economic condition precluded hospitalization in an antigen-free room at this time. On March 9, 1935, at the Nix Hospital, she was given gas-induced ether inhalation anesthesia for twenty minutes, which was followed by considerable nausea and vomiting. An immediate 25 per cent reduction in the epinephrine requirement followed. She left the hospital at the end of twenty-four hours against advice, and did not return for further treatments. One month later, on April 9, she reported the asthma and epinephrine requirements unchanged.

CASE 4.—P. S., a girl aged eight years, was first seen April 1, 1931, at the age of three and one-half years, and has been constantly under my care since. This was a case of severe polyseasonal pollen asthma. Desensitization was extremely difficult on account of an unbroken cycle of practically perennial seasonal pollens. Several one- to two-day hospital stays had been required, and on one occasion epinephrine intravenously. The epinephrine requirement varied from one to eight or nine daily dosages, with occasional periods of a few days or weeks of symptom freedom. Nasal examinations were essentially negative.

The economic condition of the patient precluded any protracted antigen-free hospitalization. On the night of April 22, 1935, after a month of from four to five daily epinephrine dosages, and after twenty-four hours of uncontrollable paroxysms not relieved by even hourly doses of epinephrine, the patient was admitted to the Nix Hospital again as an emergency case. Several doses of epinephrine during the night gave little or no relief. The next morning, however, she was some better, and according to past hospital experiences, the paroxysms would probably have cleared completely in the next twenty-four hours. With the hope of obtaining some semipermanent relief, on the morning of April 23, fourteen hours after admission, ether anesthesia was induced with ether and olive oil by rectum, one-half ounce of equal parts in the mixture, producing one hour of anesthesia. As a result, the epinephrine requirement for the succeeding three weeks was reduced to three minims every twenty-four to forty-eight hours, with only one dose in the past week (date of writing, May 21, 1935). There was no change in the home environment or in treatment methods.

It will be noted that a second anesthesia is at times required to better the partial success of the initial rectal or inhalation anesthesia. Increasing the duration of the anesthesia from ten to twenty minutes has made no difference on this point. What would be the results of a more profound anesthesia, or of several repetitions of the present method at shorter intervals, is, of course, unknown. The degree of anesthesia induced in these patients was such as, in the specializing anesthetist's opinion, would permit a simple appendectomy. Also, there was no opportunity to observe the possible additional beneficial factor of more prolonged hospitalization and limited food intake attendant upon an actual major surgical procedure.

My experience with spinal anesthesia in intractable asthma is limited to one case in which it was employed to permit the surgical removal of a ruptured appendix. There was not the slightest relief to the asthmatic state until the patient was placed in an antigen-free room two days later.

CONCLUSIONS

Prolonged relief in chronic intractable bronchial asthma lasting months, as was hoped for as a result of surgical anesthesia by ether administration, was not secured. The amount and the duration of relief obtained would, however, conservatively indicate that in surgical ether anesthesia the allergist possesses another weapon, at least in some instances, of decided value in breaking the recurrent asthmatic paroxysm habit of pollen etiology when other simpler measures have failed. This relief measure may have a far wider field of usefulness in intractable asthma of other etiologies, specific or nonspecific, and

may also explain the correction of asthma and other hypersensitivity conditions hitherto ascribed to surgical intervention, intentional or coincidental.

While ether anesthesia, both by rectum and by inhalation, has undoubtedly been previously successfully employed to relieve a severe acute asthmatic paroxysm, these cases, as far as I know, are the first instances of deliberately induced surgical anesthesia with ether for the sole purpose of securing relief of a semipermanent character in chronic daily recurring asthma, the anesthetic being administered with the patient at the time actually comfortable and completely, or almost completely, symptom free.

The author desires to acknowledge the skilled assistance, in anesthesia, of Dr. George Paschal of San Antonio and of Lt. Col. Joseph Casper, Medical Corps, United States Army.

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DISCUSSION

DR. SWINEFORD.—I think the implications in this paper are rather interesting. Many years ago Bezredka reported the ability to protect highly sensitive animals against shocking doses of antigen by ether anesthesia. Since that time, Anderson and others have reported the ability to protect highly sensitive animals by other drugs, such as chloral hydrate, which are in the category of anesthesias or sedatives.

I think it has been the experience of most of us that certain people have been relieved of asthma for varying periods following the anesthesia induced for the removal of appendices, gallbladders, etc. As far as I know, no effort has been made to work this thing out experimentally. I do not think anybody has tried to find out whether deep ether anesthesia in guinea pigs will protect them, after the anesthesia has worn off, from a titrated dose of the shocking substance. Nor has anyone tried the effect of anesthesia on a large group of chronic asthmatic individuals. I think both should be done.

I have seen one patient who was completely relieved of asthma for nine years following ether anesthesia for a gallbladder operation, performed for gallbladder disease and not because it was thought it would help her asthma.

Another case which I think is of practical interest is that of a woman who was dying, we thought, of asthma. She had a vital capacity of only 200 c.c. For the purpose of relief of bronchial spasm, nitrous oxide and oxygen anesthesia was given. Within about two minutes her vital capacity had increased from 200 c.c. to 600 c.c. and within about ten minutes, her vital capacity had increased to more than 1,000 c.c. Today, almost ten months later, she has not had a severe attack of asthma.

I do not think this problem of anesthesia is specific for ether. I think it should be investigated experimentally. I believe this type of relief should be incorporated in the group of nonspecific densensitizations.

DR. BERNTON.—Dr. Swineford has quoted the experimental evidence which possibly confirms the wisdom of Dr. Kahn's courageous therapy. After an animal is sensitized, if anesthesia be applied, the animal survives the dose which otherwise would be fatal. There are many implications in that observation.

I have had two cases of interest recently, one a young girl of thirteen years who came to me a year and a half ago with definite symptoms of pollinosis, a hangover, a perennial affair. She was given the preventive course of inoculation. On August 13, 1934, she was taken to the hospital with an acute appendix, and ether anesthesia was administered and the appendix removed. Recovery was uneventful. Ever since that operation, the child has not had a single wheeze or a single sneeze, which ordinarily had been her daily experience. While I exercise a certain amount of allergic optimism, my optimism does not lead me to believe that my treatment with pollen extracts was solely responsible for that excellent clinical result.

This very year, a young boy who received only partial treatment for his spring hay fever, the last dose administered was 200 "poly" units, a modest dose (all my doses are modest), shortly thereafter was taken to the hospital with an acute appendix. The allergy treatment, of course, was interrupted, and his results this spring have been unusually excellent. Last year his symptoms were very severe.

In Washington, D. C., we have had an unusually hectic spring—the grass pollens were very numerous. The grasses always flourish in cool weather. Dr. Swineford has said something about a long list of nonspecific measures which are employed in the treatment of nonreacting asthmas.

There is a surgeon in Washington who has made no secret about it, but he advocates (and his articles appeared in the *Southern Medical Journal*) the therapeutic removal of an appendix for the treatment of intractable asthma. A year ago I met the man who administers his anesthetics. He felt this particular surgeon had put it over the allergists because he said, "These people *are* relieved of their asthma." The fact remains, however, as Dr. Swineford has pointed out, that there is clinical freedom for varied periods of time after all surgical procedures, and it is a fair question, to what extent this relief may be due to action of the anesthetic on the nerve centers. The question we must not overlook if we follow this method is that a possible ether pneumonia may appear and make us less optimistic.

DR. WALDBOTT.—May I point out that there are patients who are sensitive to ether. I reported two such cases some time ago.* One was the daughter of a hospital superintendent who had had frequent contact with ether and developed asthma from inhalation of ether after a long interval had elapsed since the previous contact.

While there are some patients who improve after an ether anesthesia, there are others who become decidedly worse when ether is administered. I had such a case in an asthmatic patient with gallbladder disease, who had been free of asthma for some time. A few minutes after the ether anesthesia had been instituted, a severe attack of asthma developed which was followed by a long course of seizures.

*Arch. Otolaryng. 17: 549, 1933.

In my recent search for cases of anaphylactic shock, I encountered several cases of sudden death during ether anesthesia. Sensitivity to ether may or may not have been the cause.

DR. PINESS.—I fear too much credit is given to ether anesthesia in surgical cases as being the cause for improvement in the asthmatic individual. One should consider nonspecific protein reactions in the surgical case as also having a part in giving relief of symptoms. This is particularly observed in cases in which tonsillectomies, appendectomies, etc., are performed. But one must not discredit our previous experience in intractable asthma in which as a last resort ether anesthesia was given with sometimes excellent results. One should not hesitate to use ether anesthesia in the allergic individual, as bronchial pneumonia or ether pneumonia rarely occurs.

As Dr. Kahn suggested, ether in oil given per rectum would be much safer than inhalation anesthesia, but I doubt very much its value as a prophylactic measure. I feel that it is a valuable adjunct in the care and treatment of the intractable status asthmaticus.

DR. RATNER.—Dr. Swineford referred to the animal experimentation with relation to the prevention of shock after anesthesia. Several years ago Gruehl and I reported a series of studies in which we anesthetized guinea pigs, removed the uterine strip, and later gave the shock injection. In no single instance, after doing several hundred of these experiments, did the anesthesia prevent the shock manifestations.

DR. I. S. KAHN.—I have had no experience with gas anesthesia. My experience with spinal anesthesia is limited to one case, given for the surgical correction of a ruptured appendix. No relief of the asthma was secured until the patient was placed in an antigen-free room two days later.

In regard to the discussion on this paper, I am not apologizing for the small number of cases reported. They are all cases of failure by the usual methods, and any trained allergist ought not to have a large number of these cases. I am not recommending this method for routine treatment. I recognize its dangers and limitations. This was purely, I thought, an interesting clinical study that was worth reporting. The superiority or inferiority of this to other methods of nonspecific treatment is not under consideration. I am merely reporting the results of its employment in four cases.

STUDIES ON THE RELATION OF MICROORGANISMS TO ALLERGY*†

II. Rôle of Yeasts in Allergy (Preliminary Report)

Samuel M. Feinberg, M.D., and Harold T. Little, B.S.
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Henrici[1] defines yeasts as "fungi that permanently maintain a unicellular growth form, not developing mycelium." We shall adhere to this definition and not confuse with it the broad term "yeast" which is so frequently used to include also the monilia. Numerous reports are on record dealing with bacterial allergy. In recent years allergy to molds has been assuming increasing interest. It is surprising that so little has been said about the possibility of allergy to yeasts. The common usage of yeast in baking bread and crackers places this substance in the category of wheat from the standpoint of frequency of exposure. Beer and wine contain a considerable amount of yeast. The latter is also to be found in dairy products and on fruits. In the study of molds in the air by plate exposure we have been impressed also with the number of yeasts found in this manner.

The clinical literature on yeast allergy is surprisingly meager. Practically none of the books dealing with allergy mention yeast as a cause of allergic symptoms, although reference is made to it more definitely in a recent one.[2] Taub[3] reports an instance of yeast sensitiveness by ingestion. Brown,[4] in discussing sensitization to fungi, mentions several yeast reactions but does not emphasize their importance. One of us (S. M. F.) has recently tabulated a number of yeast reactions in a paper dealing with fungi.[5]

Apparently there is some experimental attempt to establish the idea of the nonantigenicity of yeast. Kurotchkin and Linn[6] in 1930 reported that they were unable to produce sensitization in animals to yeast, although they were successful in their experiments with monilia. Other investigators failed to confirm these findings. Kesten and Mott[7] in 1931, working with several strains of monilia and yeast, demonstrated that the polysaccharide fraction produces anaphylactic death in guinea pigs actively sensitized with killed homologous organisms, but an attempt to sensitize actively with the polysaccharide fraction was unsuccessful.

*From the Allergy Clinic, Department of Medicine and the Department of Bacteriology, Northwestern University Medical School.

†Read at the combined meeting of the Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., June 10, 1935.

A series of 600 patients consisting chiefly of seasonal and nonseasonal rhinitis or asthma were tested with several species of yeasts. Strains used were isolated from commercial sources or from the air. Pure cultures were chemically treated, dried, and pulverized, and the dry powder was employed for cutaneous tests. In this group 65, or 10.8 per cent, gave positive tests to these powders. Although a few of the reactions were slight and might be considered insignificant, the majority of them were decided and unquestionable. Almost invariably the patients who reacted to one species reacted to most of the other species. This relationship extended to that group of nonspore forming and air-borne yeasts known as Torulae.

In 253 patients of this series cutaneous tests were made with a variety of other fungi in addition to the yeasts. Of this number, 68 reacted to one or more types of fungi, and 28 reacted to yeasts. Of those reacting to yeasts 13 reacted to the latter without giving any reactions to other fungi. It is interesting to note that the cross-reactions of yeasts with monilia were few: in the 28 patients reacting to yeast who were tested to monilia only 3 reacted to the latter, and in the 8 monilia sensitive patients 3 reacted to yeasts. Many of the yeast sensitive patients were also sensitive to Alternaria and Hormodendrum, but the antigenic relationship to these has not been settled. The vast majority of yeast sensitive patients showed laboratory evidence of sensitization with other allergens, such as pollens, foods, epidermals, and other fungi.

We have been able to fulfill all the requirements necessary for the proof of the etiologic relationship of these organisms to the clinical symptoms. We obtained marked cutaneous reactions on repeated attempts and consistent negative results in controls. We demonstrated the tendency for the related action of related species. We produced successful reactions by passive transfer on a number of occasions. We eliminated chronic and long-standing symptoms in some patients by yeast avoidance, sometimes in as short a period as twenty-four hours. We reproduced the symptoms in these patients by a resumption of yeast-containing foods.

Our clinical observations tell us that bread is the most important source of exposure to yeast. Investigation into bakery processes discloses the fact that 1.25 per cent of yeast is added to rye bread, 1.75 per cent to wheat, and 2 per cent to whole wheat bread. This means that about one-third of an ounce of practically pure yeast, constituting a very potent and highly allergenic material, is contained in a pound loaf of bread. It may be argued that the baking of the bread destroys the antigenicity of the yeast. We have tried to answer this question by making tests with pure cultures of yeast, placed in small cellophane envelopes in the center of loaves of bread, which were sub-

sequently baked at various temperatures. We found that although there was a decreasing activity of the allergenic power with increasing temperatures, nevertheless, there was still considerable potency to the specimen thus exposed in an oven for one hour at a temperature of 450° F.

Early in our experience with yeast we were surprised to learn that the majority of white crackers on the market are baked with yeast. On the other hand, graham crackers, Ry-Krisp and practically all cookies and cake are free from yeast. The one exception is coffee cake. Beer constitutes, of course, a prolific source of yeast allergen. It is likely that the yeast in the beer is even more active because of the fact that it is in solution and the temperatures to which it has been subjected have not been excessive. The increasing tendency to consume yeast in the raw, fostered by extensive advertising, has been noted to constitute a cause of symptoms in some of our patients.

We have isolated yeasts from the air, and they have given decided positive skin reactions in patients. We are not sure whether they play an important rôle in the causation of respiratory allergy. We are employing desensitization treatment in some patients who have not responded sufficiently to the elimination of yeast-containing foods. At present we can say nothing further about this particular group.

For a number of reasons we have been unable to determine the importance of the cutaneous reaction to yeast in every one of these 65 patients. In the first place, in a number of them a follow-up and a report were unobtainable. In some others the rôle of the yeast sensitiveness could not be definitely ascertained because it was difficult to dissociate other factors in elimination and treatment in evaluation of the end-results. From these standpoints, however, this group has not offered any greater difficulties and problems than the study of any other allergen. In the analysis of reactions to foods, epidermal, and other groups of allergens, the same obstacle presents itself, namely, the inability to decide in many instances the clinical importance of the allergens. Our group showed a fair number in whom we could definitely prove that the exposure to yeast was a prime or important cause of the presenting symptoms.

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DISCUSSION

Dr. Leo H. Criep.—Will Dr. Feinberg tell us how he prepares his yeast extract?

Dr. Feinberg.—I am sure I am not presenting anything new. I am sure that any one who is doing any allergy work has noticed the same thing. Curiously enough, it has failed to creep into the literature. What is in the literature is commonly read by others and believed to be true. That is my prime reason for presenting this paper.

In regard to the preparation of yeast extract, the materials I used for testing were merely grown on favorable media, either liquid or solid, and removed from the media, dried, and submerged in 95 per cent alcohol and 1 per cent thymol. That is a favorite method used by some commercial houses for the killing of molds or yeasts. The yeasts were allowed to remain in that form for twenty-four hours. The liquid was decanted, the yeasts were dried again, and that was the material used for scratch testing. In the preparation of liquid extracts, we made the materials from the yeasts dried in that manner.

WHEAT MILLERS' ASTHMA*

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IN A study of occupational asthma occurring among wheat flour millers, the question of morphologic structure comes up just as it did in the early studies on pollen disease when the curiosity of a number of investigators was attracted to the sharp-pointed spicules of certain pollens and the absence of spicules in others. A comparison of the high incidence of sensitiveness to the spiculated ragweed pollen as compared with the much lesser incidence of sensitiveness to non-spiculated grass pollen should still cause investigators to wonder to what extent mechanical trauma plays a part in the sensitization of susceptible individuals to foreign agents. In the study of asthma among workers in wheat flour mills I have found consistently that they react intensely to the dust obtained from the first cleaning of the wheat and that in this dust sharp-pointed wheat hairs are a conspicuous morphologic structure. They are of very small diameter as compared with a human hair and are sharp pointed. From this dust can be obtained extracts which are very potent, not only in the production of positive skin tests, but also in the production of asthma when administered subcutaneously in infinitesimal doses and in the induction by subcutaneous treatment of tolerance for the dust as encountered in the mills and for the extract as shown by reduced scratch test reactions.

The potency of the extract obtained from the dust coming from the first cleaning of the wheat was very gross indeed as compared with extracts made from the germ, bran, the fungus wheat rust, and from the various grades of wheat flour and the proteins extracted from the ground-up grain of wheat. In fact, the majority of extracts obtained from the latter structures gave negative or weakly positive reactions. Extracts from bran gave the stronger tests, but not nearly so strong as extracts from the dust containing the needle-like wheat hairs. Reagins can be transferred passively from these patients to normal skins and react positively but not intensively to a filtered extract from a 1 per cent suspension of wheat dust.

I have no evidence which would enable me to distinguish between sensitiveness to wheat hairs per se and the scaly external structures of the wheat grain other than hairs. Both are found in abundance in surface wheat grain dust. I cannot exclude an idea that the sharp-pointed hairs may penetrate the mucous membranes and thus allow excitants from other constituents of the dust to enter the membranes

*Read at the combined meeting of the Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., June 10, 1935.

and sensitize people and thereafter cause reaction. This would seem analogous to the fact that scratching the skin with an instrument allows penetration of pollen extracts which can either sensitize an individual or cause reaction in one already sensitized.

We must all accept the early and indisputable studies of Cooke and Vander Veer, Coca and their associates on the hereditary factor in allergy, and the axiom which they proved that the more complete the

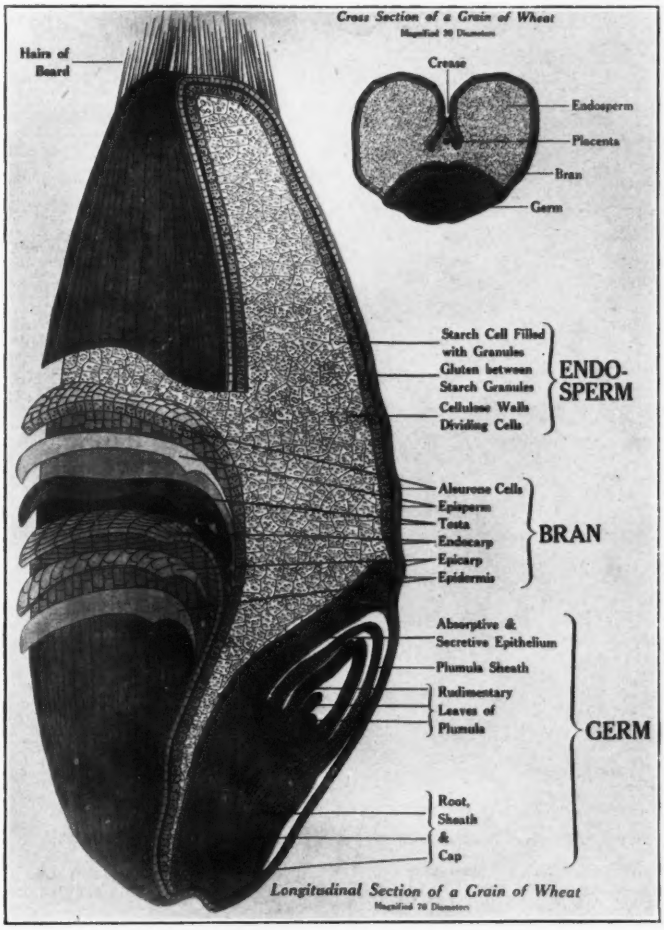

Fig. 1.—Longitudinal section of a wheat grain showing the hairs or beard of wheat.

heredity, the earlier are the symptoms of hypersensitiveness destined to appear. I believe, however, that we must direct almost equal attention to the influence of other factors such as trauma, illnesses, the effect of intoxications, and peculiarity of exposures which no doubt often determine the particular excitant to which a patient begins to react.

In the several cases of wheat millers' asthma which I studied I found a like history of the patients becoming subject to cough and asthma

while working in wheat mills, especially on windy days and especially when work or accident to the machinery of the mill caused them to be exposed to unusually large amounts of dust coming from the first cleaning of the wheat. Depending upon the degree and the duration of exposure to this dust, attacks of asthma would follow which lasted from a day to a week or more and varied from cough to marked asthma, or even to a completely prostrating asthma which was difficult to relieve by therapeutic measures. Apparently sensitization comes on after several years' work in the mills and gradually increases in severity until it resulted, in two of my cases, in an illness which caused

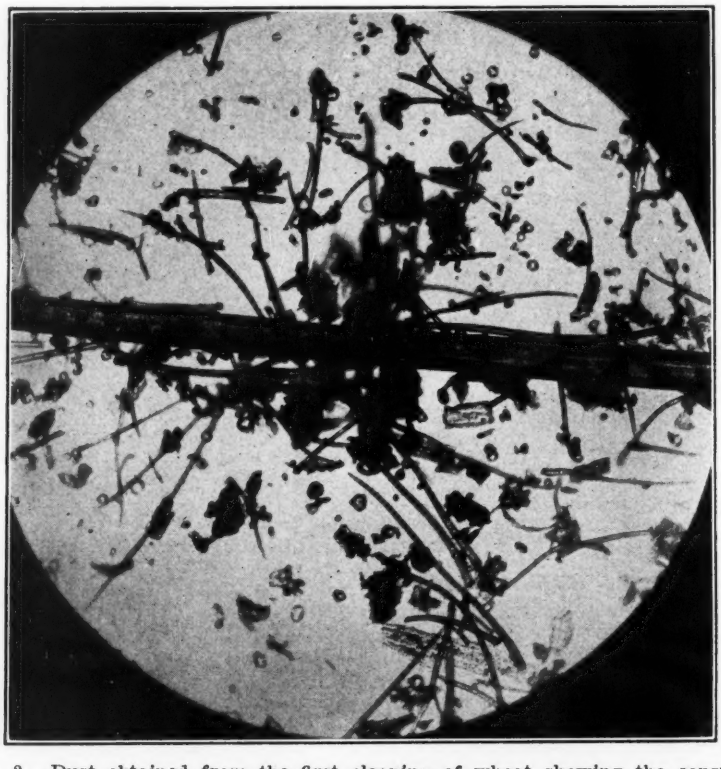

Fig. 2.—Dust obtained from the first cleaning of wheat showing the conspicuous wheat hairs which are sharp pointed and very small in diameter as compared with the human hair placed transversely across the slide.

the patients to quit the business of milling, and this in spite of treatment with the extract from wheat dust which reduced the frequency and severity of their attacks. One patient was so disabled at the age of fifty-three years by a complicating emphysema that he was granted disability insurance. This patient was not affected by any agent other than wheat dust.

COMMENT

I frankly believe that the symptoms, cough and bronchitis, in these cases were due partly to a foreign body reaction in the bronchial

membranes against the wheat hairs, which no doubt penetrated the membranes.

I once observed a case of iritis caused by hairs from a camel's-hair brush which the patient used in applying remedies for conjunctivitis. The hairs actually worked their way through the cornea and lodged in the iris and could easily be seen with a corneal microscope. The iritis was looked upon as a foreign body reaction. This is entirely aside from sensitization phenomena but could easily augment grossly the severity of symptoms caused by true allergy and account for failure of the patients to respond satisfactorily to remedies which are used successfully in the treatment of allergy.

TREATMENT

The patients under discussion could be relieved within one to several days by complete avoidance of dust coming from the first polishing of wheat. Symptoms were less severe while working in a mill if masks were used when they were exposed to the dust in certain rooms in the mill or on windy days when they would be inclined to have asthma or cough in many parts of the mill.

In one case it was necessary for the patient to change his occupation because of a complicating emphysema and in another because of a phobia which developed after several severe attacks.

In two patients treated with small ascending doses of wheat dust extract a marked increase in tolerance for wheat dust was obtained together with gross reduction in the intensity skin tests. Whether or not this method of treatment will prove to be practicable can be determined only by further work. It would not protect against gross and unavoidable exposures to dust from wheat in two cases.

CONCLUSIONS

1. Sensitization to the hairs or outer cells of wheat is, I believe, the commonest cause of cough and asthma among wheat flour millers. In this type of sensitization the patients do not necessarily react clinically nor by tests to any other fractions of the wheat grains or to wheat flour.

2. This type of sensitization is transferable passively to normal skins.

3. Continuous exposure to wheat dust over a period of years can cause emphysema and debility and may force a change in occupation in spite of therapy.

4. Avoidance of exposure in asthma caused by wheat dust is followed by rapid relief of asthma in uncomplicated cases.

5. Treatment with extract of wheat dust is partly successful but does not protect the patient against unusual exposure to wheat dust.

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DISCUSSION

DR. PARLATO.—Dr. Duke is to be congratulated for this paper because I think it is the first time any discussion has been presented here regarding what is known as plant hair. My attention to this type of allergen was aroused when a patient reported that touching the skin of a peach caused a dermatitis.

My interest particularly in wheat has been extended because of the work which has been done with insects and flies. When we speak of wheat handlers, millers, for example, I want you to recall that Buffalo is the largest milling center in the whole United States. While Dr. Duke has had two cases, we have had twelve cases of people who worked in the mills and have had asthma due to inhalation of the dust.

Several years ago Ancona reported asthma due to the wheat rust. Cadman reported similar experiences. I have made an extract of the wheat rust as sent to me by the United States Department of Agriculture. Over a period of three years, I not only tested the patients who were sensitive to the mill dust but also tested routinely other allergic and nonallergic individuals. I was unable to obtain any positive results with the wheat rust.

The other factor that must be recalled, when we consider asthma due to milling dust, is that these grains are the natural home of a great number of moths, midge flies, and other insects. Washington's records show that every year millions of dollars of damage is done to the granaries of this country by the various insects. So, in considering the etiology of millers' asthma, we must take into consideration the possibility that there have been introduced not only such factors as wheat rust but emanations and bodies of these insects and flies.

DR. LEON UNGER.—I should like to ask Dr. Duke a question about the relationship of these miller asthmas to wheat foods. What work has he done with other cereals than wheat, and what is his opinion about the result of treatments in bakeries and the resistance of bakers to work by desensitization?

DR. ALBERT H. ROWE.—Dr. Parlato's remarks reminded me of a patient who came to me two years ago, complaining of hay fever during the peach canning season. He was very sure his symptoms occurred as a result of contact with the fuzz that came off the peaches. I tested him with pollens and found definite reactions to a number, but he was sure they had nothing to do with his symptoms. I gathered a lot of the peach fuzz from the boxes and made an extract to which he gave no reaction, by either the skin or the intradermal method. I thereupon desensitized him with pollens that were in the air and those to which he gave a slight reaction which were predominant in the air at that time. The following season he had no difficulty whatsoever. It is an interesting side light on his opinion that his symptoms were due to the fuzz on the peaches.

DR. DUKE.—Asthma among mill workers is different from asthma among bakers or people sensitive to flour. Mill workers can work around flour and eat bread and have no reaction at all.

TRICHOPHYTIN HYPERSENSITIVENESS*

Report of a Case With an Immediate or Reaginogenic Type of Reaction

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As POINTED out by Sulzberger and Kerr[1] in 1930, positive skin reactions of the delayed or tuberculin type are quite common in individuals infected with the trichophyton fungus and are evidence of a hypersensitiveness or allergy to the products of this organism. The reactions are particularly prone to occur in individuals who have manifestations of this sensitiveness in other parts of the body, constituting the so-called "ids." Because of the prevalence of this type of fungus infection, or athlete's foot as it is generally known, this type of sensitivity is quite common.

Positive skin reactions of the immediate, urticarial, or reaginogenic type to an extract of trichophyton fungus (called trichophytin) are, on the other hand, quite uncommon. Sulzberger and Kerr[1] in the same article gave an account of the first reported instance of this type of reaction—intradermal injection of 0.1 c.c. of trichophytin, into an individual with dermatophytosis, was productive of an enormous wheal reaction with pseudopods and a large area of erythema within a period of fifteen minutes; in forty-eight hours the typical late or delayed reaction was also obtained. Examination of the serum for reagins by the Prausnitz-Küstner method showed the presence of circulating antibodies or reagins which were species specific for trichophytin.

No similar report has since appeared in the literature, although the occurrence of this immediate type of reaction has been noted in such other conditions as asthma.[1] In view of this, the occurrence of a similar type of reaction in an individual with dermatophytosis of five years' duration stimulated further study of this subject. These findings have proved of sufficient interest to warrant a report at this time.

Case History.—The patient, W. J. T., aged twenty-four years, has had clinical evidence of dermatophytosis of the feet since 1930 and recurring vesicular eruptions or "ids" on the hands since 1932. Except for a marked hypersensitiveness to poison ivy, both the personal and the family history were entirely negative for any evidences of allergy.

*From the Department of Bacteriology, Duke University School of Medicine; and the Department of Medicine, Temple University School of Medicine.

Experimental Studies.—Culture of the interdigital scales from the feet on a broth composed of crude dextrose 40 gm., Fairchilds' peptone 10 gm., and water to 1 liter with a pH of 5.5 showed *Trichophyton interdigitali* (Priestly strain), from which several extracts were prepared and used throughout the experiments. The following is a list of the extracts used and their method of preparation.

Extract No. 1. A three-month culture of *Trichophyton crateriforme* was passed through a sterile Zeitz filter. The residue was placed in a 50 c.c. centrifuge tube and layered over with about $\frac{1}{16}$ in. toluene, and this was allowed to stand in an incubator for twenty days, with replacement of the toluene as it evaporated. The toluene was then allowed to evaporate completely, and the residue was suspended in water and filtered through a Zeitz filter. The residue was discarded, and to the filtrate was added absolute methyl alcohol. This gave no precipitate and was removed by evaporation.

Extract No. 2. A three-month culture of *Trichophyton interdigitali* was ground in a sterile mortar with Alorundum for thirty minutes. This was taken up with the least amount of sterile water possible and allowed to stand for twenty-four hours at room temperature. It was then centrifuged for one and one-half hours and the supernatant fluid removed and bottled.

Extract No. 3. (From Bloch.[2]) A four-month culture of *Trichophyton interdigitali* was used. The fungus was fished from the broth and washed twice with sterile water. These washings were combined with the broth and evaporated down to 5 c.c. This solution was poured with stirring into 30 c.c. of methyl alcohol (100 per cent) and a precipitate obtained. This was filtered, the filtrate labelled "3-A" and saved after the methyl alcohol had been removed by evaporation. The residue (small amount obtained) was washed repeatedly with methyl alcohol to cleanse and then dissolved in 10 c.c. of sterile saline and labelled "3-C." The fungus fished out was mixed with Fuller's earth, ground, and then frozen and thawed repeatedly by means of dry ice. This was then taken up with the least amount of sterile water and filtered. The residue was discarded, the filtrate labelled "3-B." (No precipitate was obtained by adding 3-B to 100 per cent methyl alcohol up to 40 per cent of the original volume.)

Extract No. 4. A two-and-one-half-month culture of *Trichophyton interdigitali* grown on honey agar was scraped off and mixed with acetone. It was dried in vacuum and extracted with Coca's solution containing 1:5,000 merthiolate for two weeks. It was then passed through a sterile Zeitz filter and diluted with 10 c.c. of saline.

Extract No. 5. (Lederle Lab.) Original broth of a three-month culture of *Trichophyton interdigitali* was used. The broth and fungus were frozen and thawed, shaken with glass beads, ground to a paste, filtered, and diluted 1:30.

Extract No. 6. This consisted of Metz trichophytin composed of 40 per cent *T. gypseum,* 20 per cent *T. cerebriforme,* 20 per cent *T. rosaceum, violaceum* and *crateriforme* (equal parts).

These extracts were examined for protein and carbohydrate content by the biuret, Millon, and Molisch tests, and except for the commercial preparations, were diluted arbitrarily to conform roughly to those of the commercial preparations. From this the dilutions used in the tests were computed.

Skin Tests.—These were carried out by the intradermal injections of 0.1 c.c. of each extract into the skin of the patient (W. J. T.). In later tests done for confirmation in the Temple University Allergy Clinic, the amount usually employed in routine allergic skin tests (0.02 c.c.) was injected. The results of these tests are shown in Table I. In all instances the reaction, occurring within ten minutes, consisted in the formation of a large wheal, usually with pseudopods and surrounded by a large area of erythema, a reaction usually classified as markedly positive. This immediate reaction disappeared within a few hours and was not followed in twenty-four or forty-eight hours by the usual delayed reaction characteristic of trichophytin allergy.

TABLE I

		DILUTION	PROTEIN CONTENT	CARBOHYDRATE CONTENT	SKIN TEST	
Extract 1		1:20	+++	++	++	
Extract 2		1:20	+	++	+	(no pseudopods)
Extract 3						
	A.	1:10	+	++	++±	
	B.	1:20		+++	++	
	C.	1:60 (25 mg. in 10 c.c. saline)	+	++++	+++	
Extract 4		1:20	+	+	++	
Extract 5		1:30	+	0	+	
Extract 6		1:50		++	+++	

Skin tests with extracts of monilia, tuberculin, and with the broth in which the fungus was cultured, failed to elicit any response in the test patient's skin.

Skin tests repeated at intervals over a period of three years showed similar response.

Antibody Studies.—Precipitins and complement-fixing antibodies. Intravenous injections of trichophytin-Metz, beginning with 0.5 c.c. and increasing gradually to 8.0 c.c. were given at five-day intervals to a rabbit for a period of nine weeks. After the fifth week, blood was taken at weekly intervals and examined for antibodies. The rabbit showed no signs of reaction to the injections but lost weight stead-

ily and died of pneumonia without other gross visceral lesions twelve weeks after the injections were begun.

Precipitin tests performed with the usual ring technic and complement fixation tests according to the Kolmer technic were done with each serum obtained from the rabbit and also with serum obtained at three different times from the patient. Negative results were obtained in all tests.

Reagins.—The serum of the patient was collected with the usual sterile precautions, and four subjects were used for the passive transfer—one of these, E. R. P., gave no clinical history of epidermophytosis and gave both negative immediate and negative delayed types of reactions when tested intradermally with 0.1 c.c. of the trichophytin-Metz and with the culture broth. Two others, A. L. J. and P. H., had

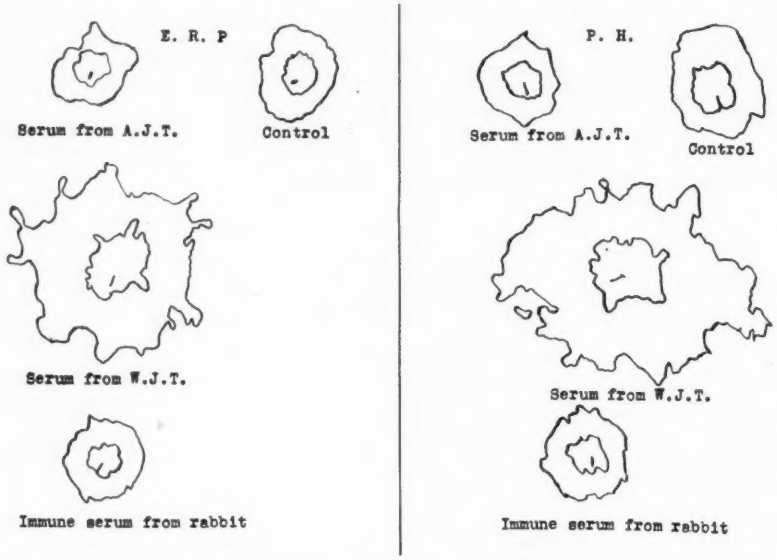

Chart 1.—Reactions following injection of sensitized site with trichophytin in subjects E.R.P. and P.H.

clinical histories of mild epidermophytosis, and a third subject, A. J. T., had marked infections of the hands and feet. All three gave negative immediate reactions to the trichophytin and to the control broth, but positive delayed reactions to the trichophytin coming on in twenty-four hours and lasting two to three days.

All four transfer subjects were then given intradermal injections in three different sites with 0.1 c.c. each of the following: (a) serum from the patient, W. J. T., (b) serum from the immunized rabbit, and (c) serum from A. J. T. the transfer subject who had such a marked clinical infection and gave the delayed type of reaction.

Twenty-four hours later all the sites were tested with 0.1 c.c. of trichophytin-Metz (the same as used in skin tests), and in each of the

four subjects 0.1 c.c. of a mixture of saline and culture broth was injected as a control site. The reactions were observed in ten minutes and in twenty-four hours.

Results.—In all the sites containing the serum of the patient W. J. T., an immediate reaction similar to the skin test occurred within ten minutes (Chart 1). No similar immediate reaction occurred in any of the other tested sites. In the subject E. R. P. no delayed reaction occurred in any of the sensitized sites or in the control. In the other three subjects, with epidermophytosis, delayed reactions occurred in all the sensitized sites and in all the control sites. These results have been checked and confirmed in the Temple University Allergy Clinic by using 4 other subjects and testing the sensitized sites with both 0.1 c.c. and 0.02 c.c. of the trichophytin-Metz.

COMMENT

From these experiments it can be seen that the patient shows as an unusual manifestation an immediate urticarial or reaginogenic type of skin reaction to trichophytin similar to that observed in the so-called atopic disorders and mediated by a similar type of antibody, namely reagin. The length of time over which persistence of the skin reaction was obtained is strong presumptive evidence of the permanency of these antibodies, in contrast to the reagins observed during serum sickness (Tuft and Ramsdell[3]). In this respect they are similar to the worm reagins described by Rackemann and Stevens[4] and by Brunner.[5] The failure to demonstrate any other type of circulating antibodies and also the failure to transfer passively any antibodies from the rabbit serum to the human skin are in accord with similar experiences with atopic reagins.

The exact significance of this type of reaction, in comparison to the usual or delayed reaction to trichophytin obtained in the other infected subjects used for transfer, is difficult to interpret in the light of our present knowledge. It is of interest that in these experiments the delayed type of reaction as with the tuberculin type of hypersensitiveness could not be passively transferred. This conforms to previous experiences with this type of allergic reaction. Also the patient W. J. T. does not manifest any delayed reaction to the trichophytin in contrast to Sulzberger and Kerr's[1] case. The exact explanation here is not clear.

It is also of some interest that the sensitivity in this case was species specific as indicated by the fact that the patient was sensitive to commercial trichophytin which contained all the species except *Trichophyton interdigitali*, the one which was cultured from the patient's lesion.

CONCLUSIONS

1. The occurrence of a specific skin sensitiveness of the immediate urticarial and reaginogenic type to extracts of trichophyton fungus has been reported in a patient with definite evidences of epidermophytosis and its corresponding "id." This is similar to that reported by Sulzberger and Kerr[1] in 1930, except that no delayed reaction occurred in the patient here reported.

2. Reagins to trichophytin were easily demonstrable in the serum of this patient by passive transfer. Precipitins or complement-fixing antibodies could not be demonstrated. Likewise attempts to demonstrate antibodies in the serum of a rabbit immunized with trichophytin, by passive transfer to the human skin were unsuccessful.

3. Attempts to transfer passively the delayed type of reaction were unsuccessful.

4. The sensitivity to the trichophytin was species specific.

5. Although the trichophytin reagins seemed to resemble the atopic reagins, their relationship to these antibodies or to atopic disorders is not yet understood. In this respect they closely simulate the worm reagins.

6. The extracts prepared from the culture broth were more potent than those prepared from the fungus. Also, the broth extracts had a correspondingly higher amount of polysaccharide content in contrast to the fungus extract. This seems to confirm the work of Bloch[2] in that the trichophytin is not a protein substance but is a nitrogen-containing water-soluble polysaccharide, and either the nitrogen-containing active principle is absorbed by the polysaccharide or the polysaccharide is an integral constituent of the trichophytin.

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PATCH TESTS WITH LACQUERS*

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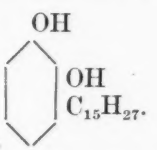
THE number of substances responsible for the production of eczema is legion. Of very practical value, of course, are those materials which are both strongly eczematogenic and commonly used. To this group, some of the lacquers certainly belong.

Lacquer eczema has been known for more than a thousand years[1, 2]; in the early days in China it was mistaken often for leprosy. In the second century B. C. crushed crab was prescribed as a specific for lacquer skin irritation, and this remedy is used in China to the present day. Kämpfer in 1712 described lacquer eczema in Europe. In 1887 Allen mentioned lacquer idiosyncrasy in natives and foreigners in Japan. In recent times attention has been called to this through contact with mah-jong sets, and also from the use of ear phones of telephones and radios and even old vases.[2-9] In a Viennese lacquer factory, using Japanese lacquer, Sachs[10] claimed he observed reactions similar to those from *Rhus toxicodendron;* he believed, but did not prove, that these were due to the Japanese lacquer.

There are essentially two groups of lacquers, the natural and the artificial, synthetic mixtures.[11, 12] In former times only the natural lacquers were used, whereas now both the natural and the synthetic lacquers are employed. The natural lacquers include tree exudations, the Japanese and Chinese lacquers, and also insect exudations, the old shellac. These substances may be dissolved in almost any type of solvent. Most of the investigations concerning the lacquers have been made with Japanese lacquer which comes from the sap of *Rhus vernicifera.* These studies have been done chiefly by Toyâma and his associates.[13-19] Toyâma found that the active principle of the Japanese lacquer was urushiol, a dioxybenzol with an unsaturated alkyl radical,



The artificial lacquers consist of nitrated cellulose, plasticizers-substances which make the film flexible and adherent, resins—usually synthetic, solvents, diluents, and pigments. It is difficult to give the composition of these mixtures, since they vary so with the whim of

*From the Dermatology Clinic of the University of Zurich, Switzerland.

each manufacturer. The artificial lacquers used in our studies contained "albertolen" (phenol derivatives) oleum lini, Chinese wood oil, turpentine or alcohol. This was the general composition of the Swiss products. It must be emphasized that these do not contain natural resins, or colophony. Because of this variance, the results of any study of lacquer dermatitis apply only to the particular type or types of lacquer used. Individuals with lacquer idiosyncrasy must be studied with the lacquer with which they worked. (Glaser,[9] Sachs,[10] Mayer,[20] Wenzel.[21]) Most observers believe, however, that turpentine chiefly and then pyridine are responsible for the skin irritations from lacquers.[20]

In this work an attempt was made to compare the eczematogenic influences of a natural lacquer and various artificial mixtures by means of the patch test. The Japanese lacquer was a 1 per cent solution in pure benzol; and the so-called artificial lacquers, an oil lacquer, a polish lacquer, and a varnish, were all applied full strength. Control tests were made in every case with pure benzol.

One hundred and fifty-nine persons were tested, the subjects varying in age from two to sixty-six years. The series included 61 eczema patients. Eczema is used in this connection as a hypersensitive skin reaction characterized clinically by vesicles and microscopically by spongiosis. This is the generally accepted European definition of the term. The control group, 98 persons, was made up of 26 patients with other skin diseases, including 8 patients with neurodermatitis, 46 patients without skin eruptions from the venereal quarantine wards, and a group of 26 medical students. In all except three of the eczema cases, and in most of the control group, patch tests were done with the routine testing materials of the clinic including *oleum terebinthinae purae*, 5 per cent formol, iodoform gauze, 1 per cent naphthalin spiritus, 1 per cent alcoholic solution of quinine, and 0.1 per cent bichloride solution.[22]

Twenty-nine of the eczema group gave positive tests to lacquer. These patients comprised masons, painters, furniture workers, cooper, gardener, molder, auto lacquer workers, iron workers, chemists, a galvinizer, and a nurse. The control group had 12 positives cases, and these included a porter, two medical students, a maid, and a physician.

Almost all the positive tests were due to Japanese lacquer alone. In the few cases in which the other lacquers were positive, Japanese lacquer was always positive. Moreover in the entire series there was only one positive benzol test, and this was in an individual who reacted strongly to all types of patch tests with the exception of tests with the physiologic solutions.[23]

Table I shows that the eczema hypersensitivity to Japanese lacquer is fairly widespread (positive tests in 25 per cent of the entire series);

whereas positive tests with the three different artificial lacquers were observed in only about 2 per cent of the cases. These facts have definite value in the prophylaxis of eczema, especially for those interested in the study of industrial eczema as applied to those who work with lacquers and those who come into contact with lacquered materials. In the eczema series there were two patients who were not only positive to Japanese lacquer but also whose eczema was very probably caused by this lacquer. In eight other cases this was a good possibility for the production of their eczema. Since the cases for this study were not selected but, as mentioned above, rather taken at random, it follows that although Japanese lacquer is not so commonly used as the artificial lacquers, nevertheless it has a definite practical value for the production of eczema.

TABLE I

FREQUENCY OF SKIN REACTIONS TO THE LACQUERS

SERIES	NUMBER OF CASES IN SERIES	CASES POSITIVE TO JAPANESE LACQUER	CASES POSITIVE TO ARTIFICIAL LACQUERS*
Total	159	41	3
Eczema	61	29	2
Control	98	12	1

*All the artificial lacquers were always positive together.

Table II reveals a frequent association of positive lacquer and turpentine test; however not all the lacquer cases by far were also turpentine positive. The positive turpentine test depends to some extent on the type of turpentine employed, since the various turpentine preparations are certainly not the same.[24] Bonnevie, Danbolt and Burckhardt[25] have studied turpentine reactions extensively. They conclude the significant fraction is the α pinen. There are also two types of skin reactions with turpentine: one, the toxic (direct irritant), and the other, the true eczematoid reaction.

TABLE II

CASES POSITIVE TO JAPANESE LACQUER

SERIES	TURPENTINE TESTED CASES			CASES TESTED TO OTHER ECZEMATOGENIC SUBSTANCES		
	TOTAL	POSITIVE	NEGATIVE	TOTAL	POSITIVE	NEGATIVE
Total	31	17	14	35	6	29
Eczema	23	14	9	29	6	23
Control	18	13	5	6	0	6

The association of Japanese lacquer and eczematoid turpentine tests could be regarded as an association of chemically related substances. It would be interesting to compare with *Rhus vernicifera, Primula obconica, Rhus diversiloba, Rhus toxicodendron, Semecarpus venosa,* and *Peroba granda amarella.* The last two are the most recent addi-

tions to the group of skin irritations from plants. In this connection interesting work[26] has been started with *Rhus toxicodendron,* and the offending agent is in the unsaponifiable fraction of the oil-soluble extract.

Bloch[27, 28] claimed that the eczema patient differed from the non-eczema patient in that the former was hypersensitive to certain "ekzemauslösende Substanzen" without these substances being related to each other. This assertion is borne out in our lacquer tests, since the eczema patient reacted four times more frequently to Japanese lacquer than the control case. In other words, the polyvalency of Bloch leads to a positive test with Japanese lacquer.

This series exhibited evidence of a long latent period until the patch test with Japanese lacquer became positive. Almost two-thirds of the positive cases occurred after twenty-four hours, and nearly one-half after forty-eight hours.

TABLE III

TIME REQUIRED FOR JAPANESE LACQUER PATCH TEST TO BECOME POSITIVE

GROUP	1 DAY	2 DAYS	3 DAYS	4 DAYS	5 DAYS	5-10 DAYS	MORE THAN 10 DAYS
Eczema	10	7	8	1	1	2	0
Control	4	5	1	0	0	1	1 (12)

If these reactions had not been observed for long periods, the frequency of the positive reactions would have been reduced considerably. Most of the tests were made on the back, but in the few cases in which the tests had been done on the arms, the relatively long latent period again was observed. No pigmentation of skin was observed with any test. A possible explanation (Toyâma and also Schaaf) is offered by supposing that it is not the Japanese lacquer which gives the positive test but some oxidation product, and a relatively long time on the skin is required for the formation of this product. A similar explanation has been proposed for ursol eczema. Another possibility is the sensitization of the skin by the patch test.

CONCLUSIONS

Sixty-one eczema cases and 98 control cases were patch tested with 1 per cent Japanese lacquer in benzol and with three types of artificial lacquers. Save for a few polyvalent individuals, all the positive tests were obtained with Japanese lacquer alone. The much greater potential eczematogenic property of Japanese lacquer over the other lacquers used in this study was demonstrated. There was noted also a relatively long period until the patch test with Japanese lacquer became positive, and the importance of the time element in the interpretation of the patch tests was shown clearly.

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Special Reports

AN AUTOMATIC APPARATUS FOR DIALYSIS*

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THE apparatus described here has been found convenient for the concentration and dialysis of aqueous colloidal solutions. It was originally designed for removing diffusible substances from urine. As a simple, rapid method for the dialysis of large quantities of fluid is highly desirable in the preparation of many allergens used for intradermal skin testing, especially fruit and vegetable juices, we employed this apparatus for that purpose. The principles upon which the method is based are (1) maintenance of the circulation of the fluid being dialyzed by a current of air and (2) concentration of the solution being brought about by hydrostatic pressure of the fluid. Growth of microorganisms during dialysis may be largely inhibited by the use of a layer of toluene on the surface of the fluid being dialyzed.

After a period of thirty-six to forty-eight hours, the fluid is removed from the apparatus and further concentrated to a convenient volume by distillation at 37° C. under reduced pressure. In this manner, we have been able to prepare active nonirritating extracts of various fruits and vegetables for use in intradermal tests of sensitivity.

DESCRIPTION OF THE APPARATUS FOR DIALYSIS

Fig. 1 is a drawing to scale of the apparatus.

A is a receiver for the liquid, *E*, to be dialyzed. It is made by removing the bottom of a 2.5 liter bottle. A layer of xylene, *D*, covers the liquid. *A* is supported on a ring-stand, on the foot of which *J* is placed.

B is a safety device to prevent excessive pressure of air. It consists of a 2 liter cylinder almost filled with water. The air is led from the pressure lines into the T-tube, *K*, from which a tube leads nearly to the bottom of *B*. By means of two screw clamps, the current of air can be so regulated that a steady stream of bubbles passes up the tube leading from the dialyzing sac, *C*. A small funnel, *F*, is provided at the top. In order to prevent a back flow of the fluid, *E*, toward *K*, in case of a leak in the air line, it is only necessary that *K* be placed on a higher level than *D*.

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C, the dialyzing membrane is made of collodion. We use for the mold a tube 200 mm. long with an inside diameter of 30 mm. The solution of collodion is made by dissolving 8 gm. pyroxylin in a mix-

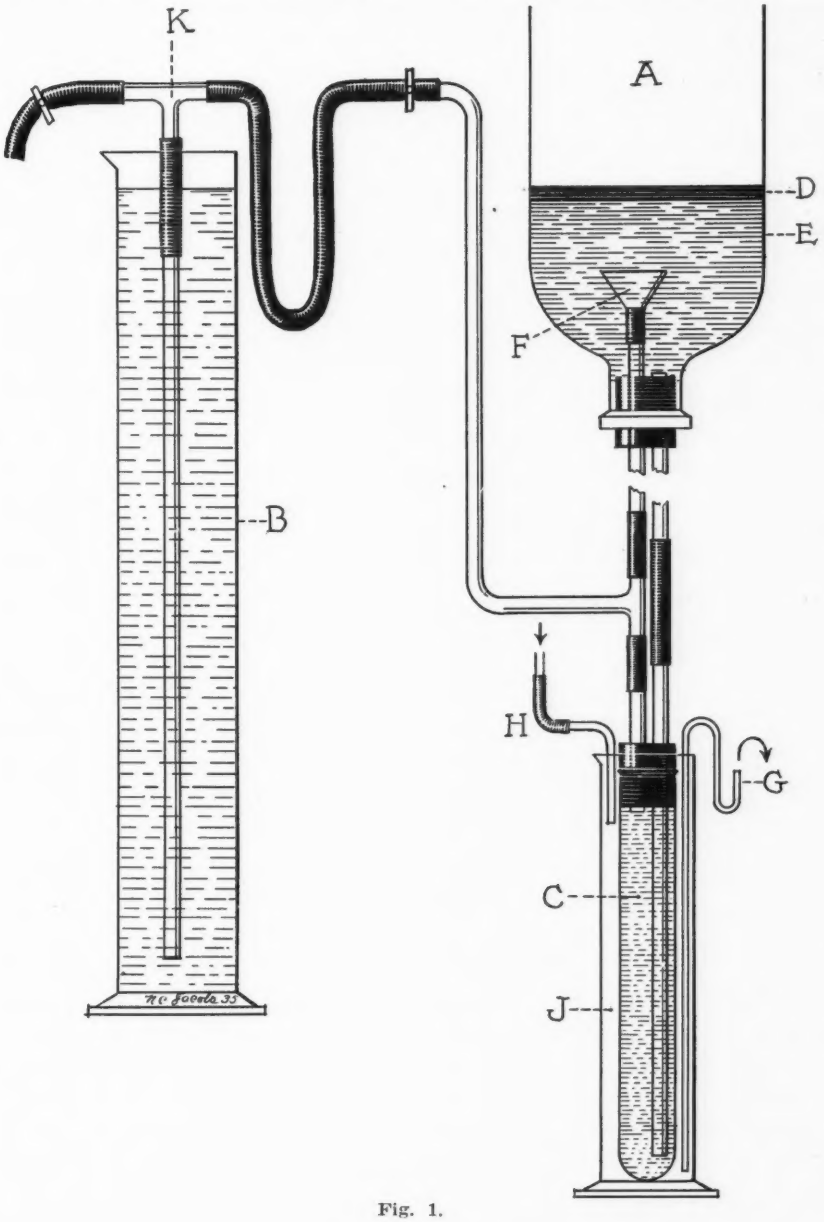

Fig. 1.

ture of 50 c.c. 95 per cent alcohol and 50 c.c. ether. The collodion solution is poured into the mold without producing bubbles. After draining, the tube is kept inverted until the odor of ether has disappeared. It is then filled with water, introduced between the collodion and the wall of the tube, and the collodion tube is removed and preserved in

water containing a little chloroform. Each tube is carefully tested for leaks. Solutions of collodion from which solvent has evaporated are unsuitable; sacs prepared from them are relatively impermeable to sucrose. The sac *C* is firmly connected to a two-hole rubber stopper by means of rubber bands. The glass tubes which connect *C* to *A* are so arranged that the fluid flows from the bottom of *A* to the bottom of *C*. The length of the tubes should be such that the surface of the fluid in *A* is about 40 cm. above the surface of the water in *J*.

J is a small cylinder containing water against which the fluid, *E*, is being dialyzed. The space between the walls of *J* and *C* should be about 5 to 6 mm. Water enters *J* through a tube *H*. The flow is so controlled that about 10 liters will flow in twenty-four hours.

G is a syphon which reaches quite to the bottom of *J*, so that the more concentrated part of the dialysate will be removed first. *G* is bent upward as shown to regulate the level of water in *J* at the middle of the rubber stopper in *C*.

DIRECTIONS FOR OPERATION OF APPARATUS

The apparatus is assembled with no water in *J*. The entire quantity of fluid to be dialyzed is then poured into *A*. When it has been ascertained that there are no leaks, *J* is filled with water. The air-flow, *H*, and the syphon, *G*, are then started. The current of air is then regulated so that the bubbles can be easily counted. If the flow is too rapid, spattering may occur. So long as the fluid in *A* is sufficiently concentrated, circulation will be kept up by differences in density alone, but in the later stage of the dialyzing, the current of air is needed for maintaining the flow, especially when the level of *E* falls below *F*. In practice we employ the air current from the beginning of dialysis.

After it is started, the apparatus needs little attention. It is only necessary to provide a sufficient flow of distilled water through *H*.

PERFORMANCE OF APPARATUS

A variety of pure aqueous solutions, free of colloids, has been dialyzed in the apparatus, in order to study the rate of decrease in their volume and in their concentration. For this purpose, small measured quantities of the solution were removed at definite times and evaporated to constant weight in weighed pyrex dishes. The volume of the dialyzing solution was determined with sufficient accuracy for our purpose by noting its level on a scale attached to the container, and previously graduated by placing known volumes of water in the apparatus. The amount of dialyzable material left in the solution was then calculated. The rate of flow of the water which bathed the dialyzing sac was kept approximately constant; at about 1 liter in two and one-half to three hours. We find that the rate of dialysis is

not materially increased by further increasing the rate of flow of the bathing water. Dialysis was continued for about thirty-six hours.

The relationship between the amount of solute remaining undialyzed and the time was plotted. From these curves we have estimated the time required for dialysis of 50 per cent, 90 per cent, and 99 per cent of the solute. The results are shown in Table I. These results may be used to compare the rates at which different solutes dialyze. It is evident that urea, sodium chloride, and glucose dialyze rapidly. In thirty-seven hours, or less, 99 per cent of these solutes may be removed from 2 liters of solution. Also, there is a considerable reduction in the volumes of the solutions of urea and of glucose. The reduction is greater than the reduction in volume when pure water is placed in the container. We find that membranes prepared from solutions of collodion from which even a small amount of solvent has evaporated

TABLE I

DIALYSIS OF CRYSTALLOIDS

CRYSTALLOID	NO. OF EXPERIMENT	VOLUME OF SOLUTION, C.C.		SOLUTE, GM.		WATER USED	DURATION OF EXPERIMENT	TIME REQUIRED FOR REMOVAL OF INDICATED AMOUNT OF SOLUTE, HOURS		
		INITIAL	FINAL	INITIAL	FINAL	LITERS	HOURS	50%	90%	99%
None (water)	W_1	1000	330			2.4	10.0			
	W_2	1000	425			3.6	31.0			
Urea	U_1	1000	130	29.8	0.15	10.0	31.0	3.7	10.3	24.1
	U_2	1000	130	26.4	0.16	3.4	33.6	5.4	14.3	27.5
Sodium chloride	S_1	793	450	89.0	1.26	12.5	28.0	4.3	14.3	26.7
	S_2	800	456	42.3	1.07	7.0	31.0	6.3	20.1	36.7
Glucose	G_1	800	208	76.2	1.26	9.3	31.5	4.6	16.8	33.3
	G_2	1000	98	95.0	0.48	5.1	23.8	2.5	13.3	22.7
Cane sugar	C_1	800	92	78.2	0.26	3.3	48.8	7.8	27.5	43.3
	C_2	800	525	78.8	8.98	16.7	50.8	25.0		
	C_3	1500	160	161.0	2.5	8.1	28.4	8.0	21.7	30.0
	C_4	1500	225	163.8	1.3	15.8	47.4	11.0	26.6	43.0
	C_5	1500	810	150.5	12.9	17.2	57.3	19.5	52.8	
	C_6	1500	950	128.5	23.2	15.4	48.1	24.3	61.7	
	C_7	1500	1050	163.0	35.4	12.3	35.1	16.5		
	C_8	1500	950	161.0	32.5	6.8	34.3	18.1		

are relatively impermeable to cane sugar. For this reason, we have made a more detailed study of the conditions which affect the rate of dialysis of solutions of cane sugar. In the experiments numbered C_1 and C_3, the membranes were made from freshly prepared collodion. In these experiments 50 per cent of the solute was removed in about eight hours. In other experiments (C_2, C_5, C_6, C_7, C_8) the membranes were all prepared from older solutions of collodion and were much less permeable. On the average, twenty-one hours were required to remove 50 per cent of the solute. The collodion used for experiment C_3 was kept at room temperature, tightly stoppered with cork, for

eight days. After this interval, a membrane was prepared for experiment C_4. Two weeks later, a membrane was prepared for experiment C_5. The decrease in permeability is obvious. We, therefore, recommend that solutions of collodion be kept not longer than a week at room temperature if the sacs prepared from them are to be used for solutions likely to contain cane sugar. In experiments C_7 and C_8, the same membrane was used. The average hydrostatic pressure in experiment C_7 was 40 cm., and in experiment C_8, it was 55 cm. The results are substantially the same. It is, therefore, unlikely that the defects of an impermeable membrane can be overcome by increasing the hydrostatic pressure by a moderate amount.

TABLE II

INITIAL VOLUME	VOLUME REMAINING	HOURS ELAPSED UNTIL CL FREE
Urine c.c.		
1000	200	48
1880	?	48
575	?	–24
630	400	24
1055	275	–48
670	?	24
900	?	36
1060	490	58
670	?	36
630	450	48
570	400	48

Table II shows that chlorides may be removed from urine by dialysis in this apparatus. It is also possible to remove reducing carbohydrates from fruit juices (Table III). We have ascertained that allergens are not lost during dialysis.

TABLE III

SUBSTANCE & VOLUME	VOLUME REMAINING	HOURS ELAPSED UNTIL FREE OF REDUCING SUBSTANCES
Tomato juice 720 c.c.	(Water added, amount not determined to get volume great enough to test for CH without dismantling apparatus. Therefore it is not known how much volume shrank.)	60 hours
Orange juice 654 c.c.	30 c.c.	About 96 hours

The experiments recorded above show that certain crystalloids may be removed in a satisfactory manner from solutions containing no colloids or only small amounts of colloids by the simple apparatus described. We are undertaking a study of the dialysis of colloidal solutions in order to make certain that no great loss of such colloid occurs during the process and that the removal of crystalloids is not greatly

retarded by the colloids. At this time we can only state that the apparatus has been of service in preparing allergens of marked activity, relatively free from crystalloids.

SUMMARY

An apparatus is described for the automatic dialysis and reduction in volume of aqueous solutions of urine and of vegetable and fruit juices. The apparatus is automatic in action, requires little attention while in operation, and is readily constructed from material available in most laboratories.

TREATMENT OF ALLERGIC PATIENTS WITH ADDED SKIN REACTIONS*

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IN THE examination of allergic individuals one is frequently confronted with positive skin reactions some of which are significant while others are apparently irrelevant.

In a recent study (unpublished)† the following facts were revealed: First, some individuals were encountered who had symptoms due to pollens of one season and skin sensitivity to pollens which bloom at another season, but which caused no symptoms. Second, of 154 patients, approximately one out of every 18 developed symptoms the following year to pollens to which he was formerly only skin sensitive. Third, of individuals who were skin sensitive to pollens only of one season, one patient in 254 developed symptoms to an additional pollen to which he was skin sensitive, at a different season, the following year.

At present, the treatment of a patient having seasonal hay fever, and also having positive skin reactions without symptoms to pollens of another season, usually consists of combating the particular agent alone causing symptoms.

In an effort to protect such patients from pollens of an additional season the patients were hyposensitized with extracts of all important pollens to which they were skin sensitive. Some were treated preseasonally while others were treated perennially.

CASE REPORT

The following case illustrates the procedure employed. A. B., white, male, aged forty-four years, had had symptoms of hay fever for the past four years beginning about the middle of August and lasting until about the first frost. There were no symptoms at any other time of the year. His past history was negative for allergic manifestations. His son, aged thirteen years, has asthma; a daughter, aged five years, has urticaria. Intracutaneous skin tests Feb. 5, 1934, with pollen extracts containing 0.0005 mg. total nitrogen per c.c., showed the following reactions: timothy ++, orchard grass ++, June grass +++, English plantain +++, short ragweed +++, giant ragweed ++. He was treated as follows:

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†From a review of the records of patients treated in the protein clinic of Johns Hopkins Hospital over a five-year period under the direction of Dr. Leslie N. Gay. There were also included patients treated privately by Dr. Gay, by whose kind permission these data are available.

	Timothy and Plantain	Ragweeds of Each 0.00005
Feb. 6, 1934	of Each 0.00005 mg. Total N per c.c.	Mg. Total N per c.c.
	0.1 c.c. "	0.1 c.c. "
Feb. 10	0.2 c.c. "	0.2 c.c. "
Feb. 13	0.4 c.c. "	0.3 c.c. "
Feb. 17	0.6 c.c. "	0.4 c.c. "
Feb. 20	0.1 c.c. AA 0.0005 mg. Total N per c.c.	0.6 c.c. "
Feb. 24	0.2 c.c. "	0.8 c.c. "
Feb. 27	0.4 c.c. "	0.1 c.c. AA 0.0005
March 3	0.6 c.c. "	Total N per c.c.
		0.2 c.c. "
March 6	0.1 c.c. AA 0.005 "	0.3 c.c. "
March 10	0.2 c.c. "	0.4 c.c. "
March 13	0.4 c.c. "	0.6 c.c. "
March 17	0.6 c.c. "	No Ragweed Because too Great a Vol.
March 20	0.1 c.c. AA 0.05 "	0.8 c.c.
March 24	0.2 c.c. "	0.1 c.c. 0.005 Mg. Total N per c.c.
March 27	0.4 c.c. "	0.2 c.c. "
March 31	0.6 c.c. "	0.3 c.c. "
April 3	0.8 c.c. "	
April 7	0.1 c.c. AA 0.5 "	0.4 c.c. "
April 14	0.2 c.c. "	0.6 c.c. "
April 21	0.2 c.c. "	0.8 c.c. "
	Timothy and Plantain AA 0.5 mg. Total N per c.c.	Ragweeds, of Each 0.05 Mg. Total N per c.c.
April 28	0.2 c.c. AA 0.8 mg. Total N. per c.c.	0.1 c.c. "
May 5	0.2 c.c. "	0.2 c.c. "
May 12	0.2 c.c. "	0.3 c.c. "
May 19	0.2 c.c. "	0.4 c.c. "
May 26	0.2 c.c. "	0.5 c.c. "
June 2	0.2 c.c. "	0.6 c.c. "
June 9	0.2 c.c. "	0.7 c.c. "
June 16	0.2 c.c. "	0.8 c.c. "
June 23	0.2 c.c. "	0.1 c.c. AA 0.5 Mg. Total N per c.c.
June 30	0.2 c.c. "	0.15 c.c. "
July 7	0.2 c.c. "	0.2 c.c. "
July 14	0.2 c.c. "	0.2 c.c. "
July 28	0.2 c.c. "	0.2 c.c. "
Aug. 11	0.2 c.c. "	0.2 c.c. "
Aug. 18	0.2 c.c. "	0.2 c.c. "
Aug. 25	0.2 c.c. "	0.2 c.c. "
Sept. 1	0.2 c.c. "	0.2 c.c. "
Sept. 8	0.2 c.c. "	0.2 c.c. "
Sept. 15	0.2 c.c. "	0.2 c.c. "
Sept. 22	0.2 c.c. "	0.2 c.c. "
Sept. 29	0.2 c.c. "	0.2 c.c. "

This patient when retested after injections showed the same positive skin reactions except that to orchard grass, which was only one plus. He is now being treated perennially at intervals of two weeks with 0.2 c.c. of the timothy and plantain mixture and also 0.2 c.c. of ragweed extract.

Sixty patients having added as well as symptomatic reactions were so treated. All had either asthma or rhinitis, or both, during the early summer or autumn. Of these, not one developed symptoms to the pollens of an additional season (Table I). Of the patients treated in this manner, 13 per cent lost their added skin sensitivities.

TABLE I

THE RESULTS OF TREATMENT WITH EXTRACTS OF ADDED SKIN REACTIONS

Number of patients having spring asthma or sneezing due to grasses or plantains or both and having added positive skin reactions to ragweeds 32	Treatment with ragweed, timothy and plantain 32	Symptoms at ragweed season 0	Loss of skin sensitivity to ragweed 4
Number of patients having fall asthma or hay fever due to ragweeds and having added positive skin reactions to grasses or plantain or both 28	Treatment with ragweed, timothy and plantain 28	Symptoms at timothy season 0	Loss of skin sensitivity to grasses and plantain 4
Total 60	Total 60	Total 0	Total 8

CONCLUSIONS

1. Of patients who react positively to pollens of one season and have symptoms, but who have also a skin sensitivity to pollens of an additional season, approximately 5.5 per cent will develop symptoms to the latter the following year.

2. Patients hyposensitized against all important pollens to which they are skin sensitive remain symptom free from the pollens to which there are added skin reactions.

3. Thirteen per cent of patients who have added skin reactions to pollens and are treated with corresponding extracts lose their added skin sensitivity the following year.

Society Proceedings

COMBINED MEETING OF THE ASSOCIATION FOR THE STUDY OF ALLERGY AND THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

ATLANTIC CITY, N. J., JUNE 10 AND 11, 1935

A Mechanism of Protection Produced in Hay Fever Patients by the Injection of Pollen Extract. ROBERT A. COOKE, JAMES BARNARD, SELIAN HEBALD, AND ARTHUR STULL, New York, N. Y. (Abstract.)

Hay fever represents a form of clinical allergy characterized by (1) an immediate attack of coryza following contact with the proper pollen, (2) an immediate reaction on skin test, and (3) the ability of the serum of patients specifically to sensitize normal skin.

By the passive transfer of sensitiveness first demonstrated in 1921, Prausnitz-Küstner explained in part at least the mechanism of this type of allergy. The mechanism of protection afforded by pollen injections has not been explained, although the efficacy of this procedure is generally granted as a result of many years of clinical treatment.

We began our study of a protective mechanism four years ago on the assumption of a positive immune factor, and our first procedure was to note the clinical effects of transfusion using treated, hence theoretically immune cases as donors for patients with active symptoms in the beginning of the hay fever season.

In 1931, 1932, 1933 and 1934 twenty cases have been transfused and results carefully noted. No other treatment was used. Sixteen cases showed satisfactory results. Subcutaneous injection of the assumed immune serum also gave definite improvement in 60 per cent of 96 patients.

These results, in some cases quite startling, indicated the presence of a passively transferable immune type of substance in the blood which we then sought to demonstrate by serologic studies. Detailed presentation will be made of the serums of eight patients studied before and after treatment. The patients were thoroughly treated and had excellent clinical results.

By increasing dilutions of the serums, it can be shown that in six of these cases the skin sensitizing antibodies were practically identical before and after treatment. In two, these antibodies were slightly increased after treatment. Obviously desensitization was not accom-

plished, and, by the same token, results could not be ascribed to an increase of the circulating sensitizing bodies.

Then by the method of passive transfer to normal skin donors, using serum and ragweed mixtures, it can be shown that pollen extract does not desensitize the sensitive serum of treated patients; whereas it does desensitize serum of untreated subjects. In other words, in serum of treated patients there appears to be an immune body that blocks the antigen from the antibody in the cell.

Although it has already been shown that the sensitizing antibody is in the globulin fraction of serum, our studies have shown that it is in the pseudoglobulin fraction. We have not been able to demonstrate the immune body in the albumin or euglobulin fraction when these have been repeatedly reprecipitated to purity.

Attempts to separate the immune substance from the sensitizing substance are not complete, but we have been able to show that the immune substance in ragweed treated cases is specific for ragweed and does not affect timothy extract in timothy sensitive serum, but is not specific for the giant as against dwarf ragweed.

DISCUSSION

Dr. Leslie N. Gay.—In the first premise of Dr. Cooke's paper, he mentioned that desensitization probably does not occur in the treatment of individuals who are sensitive to ragweed extract. During the last few years, I have been more impressed than previously that a number of patients who have taken prolonged series of perennial treatment, not only have become symptomatically free, but also have lost the power to transfer reagins to normal recipients. Incidentally, I should prefer to use the word "recipient" rather than "donor." I believe it is confusing to use the word donor in Dr. Cooke's paper. Too much importance is sometimes attached to the skin as the medium which will tell us whether or not desensitization actually occurs. It is well known in the treatment of tuberculosis of the eye, for example, that if large doses of tuberculin are given, a very fulminating reaction in the eye is produced, the sensitivity of that individual having previously been determined by the skin test. After, however, giving that patient or another patient small doses of tuberculin, and gradually increasing the amount, we can then reach that maximum amount of tuberculin without reaction, and we can continue to give the large doses of tuberculin over a period of years with complete cessation of flare-ups in the eye, but it is difficult to change the skin reaction in that individual.

It is my impression that perhaps we do locally desensitize the organ which manifests the disease, such as the eye, without definitely changing the skin which is our medium of sensitization, or in our diagnostic study of determining the sensitization.

Of course, there are some differences in the two mechanisms. Animal experimentation in guinea pigs, however, has shown definitely that if a guinea pig has been inoculated with tuberculin and large doses are given, the lung blows up and the animal dies quickly. If small doses

are given, the animal can be desensitized, and as many as 3,000 to 4,000 doses of old tuberculin are required to produce such a result.

The question arises in my mind as to whether or not we are at present giving large enough doses. It is, of course, rather guardedly that I would suggest we go any further with large doses to prove this point, as the danger of reaction, of course, is always in mind. Still we do produce in our ragweed patients the cessation of symptoms without changing in many instances the skin reaction.

While I am not asking these questions for an answer, still there is the question as to whether we could advance an explanation that this treated serum, the "P" serum ragweed mixture, produces no immediate reaction because the immunizing "P" serum temporarily at least neutralizes the reagin. This explanation might parallel the reaction that one encounters in the toxin-antitoxin mixture which occasionally produces horse sensitivity.

If we omit the theory that a third body is produced, this so-called blocking body Dr. Cooke has mentioned (I am afraid he answered my question), then I should like to ask this question: If in his untreated case his combination of ragweed and antibody gives a reaction when first injected because of the fact that he has an overwhelming amount of ragweed, then when he injects his second dose, no reaction occurs because he has consumed his antibody. When he takes his treated serum and his antibody mixture and injects it, there is no reaction because overnight the antibody and ragweed have neutralized. Then he injects the second dose of ragweed and obtains a reaction because there has been an overabundance of antibody production or reagin production, and, therefore, he gets a secondary reaction. He answered that, I think, by saying he tried this injection in hay fever subjects and still obtained a very large reaction.

We might then bring up Landsteiner's work. I think he was able to change, chemically, antibodies and bring about an altered response. It is conceivable that by our treatment we have chemically, temporarily, changed our reagins, and thus, after a forty-eight-hour lapse, the normal cell reaction of the individual who is receiving the serum brings about a more normal state and thus a secondary reaction occurs.

DR. ALEXANDER.—I think every one will recognize that this is an extremely important piece of work and one which should seriously engage our attention.

In discussing what happens, one must consider the other side of the equation, that is, the response of the tissues to the material injected. Is it possible that there is not a block at all, but an inability of the tissues to form H-substance? The way to find that out is to inject histamine, atropine or some other wheal-forming substance. This may answer the question whether there is a block or an inability of the tissues themselves to form histamine.

DR. WALDBOTT.—Within the past year and one-half I have used convalescent serum in the treatment of patients with asthma, hay fever, and eczema in whom the ordinary therapeutic measures had not been fully adequate. I considered this treatment, in a certain sense, specific, assuming that in the average case of cured asthma or eczema a large number of individual antibodies are present in the blood which are

protective against the most common antigens, such as ragweed in asthma and hay fever, and such as milk, wheat, etc., in eczema. I used only 1 c.c. to 25 c.c. of convalescent serum intramuscularly after a preliminary skin test with the donor's serum. I had some striking results with these small quantities of convalescent serum. In some of the patients the relief was immediate, the asthma clearing up right in the office. I have had no patients, however, in whom I felt that the relief was permanent. The effect of the serum did not seem to depend on the degree or the duration of relief which the donor had enjoyed, nor on the amount of extract with which the donor had been built up. On the other hand, there were some patients who were decidedly aggravated. I found that certain serums had an injurious effect on all patients in whom it was used. If the previous skin reaction was positive, usually better results were obtained with the serum.

Among the eczema patients the benefit obtained was most striking. In these patients recurrences were not so frequent as in the asthmatic persons. I have used blood transfusions in a very small group, insufficient in number to warrant a conclusion. Perhaps the larger quantities of blood used by Dr. Cooke and his more careful selection of donors account for the better results which he obtained.

DR. TRASOFF.—I just want to ask one question. A number of years ago, while discussing with Dr. Coca the question of what is the mechanism of protection by pollen treatment, he told me he thought something is brushed away by the pollen injection, and in this way some protection takes place. Albus, in the February issue of *Zeitschrift f. d. ges. experimentelle Medizin*, expresses the same idea. He thinks that the introduction of the pollen neutralizes the cellular antibodies. If an allergen is then introduced, namely, by inhalation, it finds no reactive counterpart. In other words, there is no antigen antibody reaction, and allergic manifestations do not develop. Dr. Cooke, by injecting 500 c.c. of blood surely introduces more complement. Would that not disprove Albus' theory of so-called desensitization?

DR. SULZBERGER.—Dr. Cooke said that there were no analogies between this phenomenon he describes here and previous immunologic observations. I should like to recall the experiments with anticutins, in the case of tuberculin hypersensitivity. As far as I can see, there is close analogy between the presenter's results and the finding of neutralizing antibodies in the serums of patients immunized or spontaneously immune to tuberculin. These anticutins neutralize the effects of the tuberculin when mixed with tuberculin in vitro and then injected in tuberculin hypersensitive skins. These substances have been studied carefully by Fellner, Picker and Martenstein, Loewenstein, W. Jadassohn, and others. It seems to me that there is here some analogy, although I do not want to say that the tuberculin anticutins are identical with the bodies found by Dr. Cooke and his collaborators.

I further think that the experiments with Ascaris antigen and the neutralization of the antigen with the reagin in vitro as first demonstrated by W. Jadassohn is also an analogy. In those experiments the reagin is mixed with the antigen in vitro, and one has a reagin excess which neutralizes the Ascaris antigen. This mixture, therefore, no

longer produces immediate reaction when injected into a normal, hypersensitive or passively sensitized skin site. When that site, however, is tested forty-eight hours later (just as in Cooke's cases), with renewed application of Ascaris antigen, reaction is produced; this is due to the sensitizing action of the excess reagin. It seems to me that these findings are at least analogous to the reported results of Dr. Cooke and his coworkers.

DR. COOKE.—It has been very interesting and instructive to hear this discussion because we have had some difficulty in the interpretation of our own results.

Dr. Gay's point about the question of desensitization, I believe, is extremely well taken. The fact is that we do get excellent clinical results in patients who show no diminution of skin test or eye test, and no diminution of the sensitizing antibodies in the blood serum. So that, although continued treatment may bring about situations that are entirely different, we feel we have explained the nature of protection in the particular individuals studied. These had been treated. Their clinical results were good and they still showed humoral and cellular sensitization; in other words, they were not at that time desensitized by the pollen injections of the same magnitude as those used by Brown and Harley.

Dr. Alexander's question as to the reaction to histamine, or the possibility of explaining absent reaction in posttreatment serum-allergen mixtures on the basis of an antihistamine or a histamine neutralizing capacity, is again very important and interesting. We have not yet done the histamine tests, but if this were the explanation, then it is unlikely that there would be a specific effect of the inhibiting substance; but we have shown that there is and that the ragweed inhibiting substance does not inhibit timothy extract; and further, if this were the case, the sites must have been used up in the reaction producing histamine and we have shown that they are not.

I did not present these cases with transfusion as at all a method that we advocated on account of its great efficacy. It was not only difficult to have a sufficient number of blood donors who are willing to do this, but to find the right patient at the right time. Then to be able to carry out this procedure is so fraught with difficulties that it removes it from the realm of extremely practical procedures, and we used it only in a preliminary way to indicate the possibility of a transferable immune substance. We do not and did not then advocate it as a new therapeutic procedure. Those transfusions were made from donors on whom we had at the time no method of determining their immunity, but they were themselves still skin sensitive, and they were then also able to transfer sensitization to the skin of normal donors at the time of transfusion.

Dr. Trasoff mentions the question about the desensitization. It is true that in a recent publication, Albus resorted to a procedure in which he was titrating the natural hemolysin of human blood for sheep cells, and his results suggest that there is some modification after pollen therapy in the cases in which he studied the blood before and after the treatment, but the results, it seemed to us as we studied them, were not entirely well controlled on account of the well-known anticomplementary action of the extracts that are being used. Titrat-

ing for a hemolyzing antibody, which it seems to me has no connection with the skin-sensitizing substance which is the important factor in the production of these reactions in hay fever, has no bearing on the case, unless one believes in the so-called unitarian theory of all antibodies.

I am not familiar with the work mentioned by Dr. Sulzberger and do not know whether they are or are not analogous. I understood him to say that there was a combination of Ascaris antigen and the antibody in vitro. That, however, is a thing that we feel we have already shown does not exist here. When one takes a mixture of antigen and serum and incubates it, there is no obvious precipitation reaction, there is no flocculation, there is no evident neutralization because that extract when diluted down into proper strength can be tested side by side with the straight ragweed extract or with the combination of the ragweed serum taken before treatment, and the cutaneous reactions in all sensitive cases are analogous. So we do believe that there is no chemical or biologic attachment or binding in the mixtures and no lytic phenomenon that destroys the ragweed extract.

Department of Reviews and Abstracts

Selected Abstracts

Therapeutic Use of Localized Allergy. Garvin, P. D., and Frumess, G. M.: J. A. M. A. **104**: 2333, 1935.

The authors observed a boy of eleven years with a large ulcer over the middle of the anterior surface of the left tibia. This resulted from secondarily infected vesicles of chickenpox. The ulcer had been treated for two months in the surgery clinic but with no improvement. He was sent to the dermatology clinic, where a negative history for allergy was obtained. They made use of the Prausnitz-Küstner passive transfer reaction, as demonstrated in normal individuals in whom food reagins injected into the skin become active when the specific food is eaten. The patient was put on an egg-free diet for two days, and then 0.1 c.c. of serum obtained from a girl very sensitive to egg was introduced intradermally at each of four equidistant sites just outside the area of inflammation and about one-half inch from the edge of the ulcer. Forty-eight hours later the patient was given three soft-boiled eggs. Within forty-five minutes he complained of itching and burning in and around the ulcer. Within two hours the injected area was red and edematous, and the erythema and swelling spread until it almost circumscribed the leg. In twenty-four hours the reaction had completely subsided, and the ulcer was considerably reduced both in area and in depth. No other treatment except cleansing with physiologic salt solution was used. Within seven days the surface of the ulcer was level with that of the surrounding skin, and complete healing occurred in seventeen days.

Allergy in Migrainelike Headaches. Sheldon, J. M., and Randolph, T. G.: Am. J. M. Sc. **190**: 232, 1935.

One hundred twenty-seven patients seen at the University Hospital at Ann Arbor during the years 1931 to 1934 were studied. Among other data it was noted that a familial history of allergy was found in 81.6 per cent, mostly on the maternal side. Migraine, however, accounted for the great majority of familial instances, and it must be assumed that all such migraine was allergic. Hay fever, asthma, eczema, and urticaria occurred in a much smaller number, and these manifestations likewise occurred in comparatively few instances as collateral disturbances in the patients. The order of incidence of posi-

tive skin tests was as follows: grains (chiefly wheat), coffee, tea, celery, berries, onion, peanut, radish, cabbage, cocoa, milk, tomato, date, spinach, and carrot. This varied considerably from the order of incidence of foods suspected by the patients. By elimination diets, 18 per cent secured complete relief, 20 per cent excellent relief, and 14 per cent good relief.

Catgut Allergy. Babcock, W. W.: Am. J. Surg. **27**: 67, 1935.

From commercially prepared catgut (sheep gut) a histamine-like substance may be isolated (Gruskin). Allergic reactions may be due to foreign protein (sheep), a toxic substance (histamine) or possibly to bacterial products, since intestinal tissue is difficult to sterilize. Allergic reactions to catgut may seriously interfere with the union of tissue. They occur particularly after thyroidectomy. Here, after seven to ten days, the scar widens, becomes edematous, and unless opened, the margins may separate and discharge bloody serum. In the course of several weeks the reaction subsides, and healing is completed with a wide scar. This reaction has been attributed to various causes and has been treated with irrigations, extra sutures, etc., without effect. The same lesions, although more concealed, occur with deeper operations.

Allergic reactions to catgut were studied by burying short sections in sterilized skin. This was done in more than 120 patients with both plain and chromic gut, silk, horsehair, dermal sutures, silver wire, and alloy wire. From catgut a flare and wheal appear within twenty-four hours if the skin is sensitive. By the end of a week, sufficient necrosis occurs to canalize the part, the lining of the canal being formed by granulating and necrotic tissue. With silk the reaction is much less marked. With silver wire and alloy steel wire the reaction is minimal.

Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum. Friedman, H. J.: New England J. Med. **212**: 10, 1935.

A six-year-old boy with asthma and eczema received an injection of diphtheria toxin-antitoxin mixture twenty days previous to the presenting manifestation. Six days later he had a severe asthmatic attack lasting three days. Three days after that, there was a severe urticarial reaction. The patient was tested for sensitiveness to horse serum by the injection of 0.05 c.c. intracutaneously. Two minutes later a large localized wheal appeared, and urticaria developed on the face and trunk. Five minims of adrenalin chloride were injected subcutaneously. One minute later the child doubled up with abdominal pain. In a few seconds he became intensely cyanosed and respirations ceased.

Further injections of adrenalin both subcutaneously and into the heart, manual artificial respiration and then the Drinker apparatus were all ineffective. The child died eight minutes after the horse serum had been injected. Necropsy was not done.

Atypical Hay Fever Seasons: Their Significance in Treatment. Feinberg, S. M., and Durham, O. C.: Ann. Int. Med. **8**: 1282, 1935.

The authors stress that the successful treatment of hay fever depends upon a careful botanical investigation of the district in which the sufferer resides. Such data, even though obtained over a number of seasons, may fail in unusual years because of unusual weather conditions.

The events in the Chicago area during the 1934 season would indicate that positive skin tests to tree and chenopod pollens (Russian thistle, lamb's-quarters) should lead to the serious consideration of treatment with such pollens in spite of the fact that the individual has usually had only minor symptoms. If such preseasonal treatment is not undertaken, then during an unusual season these pollens may become very important. The same principle holds true for any district in which minor pollens are seldom considered in treatment.

The data presented show that it is an extremely hazardous procedure to predict the severity or the date of onset of a hay fever season, and stress the importance of local botanical surveys and particularly of counting and reporting the varieties and amounts of atmospheric pollen for every day during the season.

Studies on Anaphylaxis with Pollen. Bernstein, C.: J. Exper. Med. **61**: 149, 1935.

Six guinea pigs were sensitized by three injections of whole horse serum at intervals of four days. After three weeks these and six normal guinea pigs were given three injections of pollen extract (burweed marsh elder) at four-day intervals. At the same time, twelve normal guinea pigs were injected with three inoculations of equal parts of horse serum and pollen extract, and a fourth group of six animals was sensitized by injection of horse serum alone. Three weeks after the final inoculation, the precipitins for pollen extract and for horse serum were investigated, and the anaphylactic response to these substances was studied. It was found that guinea pigs injected intracutaneously and subcutaneously with extract of the pollen in relatively small amounts, did not show anaphylactic response to intravenous shock doses of this material three weeks later. If, however, the animals were sensitized with horse serum, either before or along with the same pollen injections, they could then be shocked after an interval of three

weeks with pollen extract alone. It appears, therefore, that the injection of horse serum together with pollen makes the animals much more susceptible to shock.

Specific Allergens in the Detection of the Cause and in the Treatment of Rheumatism and Gout. Gudzent, F.: Deutsche. med. Wchnschr. **61**: 901, 1935.

The author saw a patient with gout who had attacks whenever he took treatment with milk. This led to the suspicion of an allergic process; whereupon, after inquiry, it was found that other patients with rheumatic disturbances stated that they felt worse after taking certain foods. Skin tests to these allergens were positive, and abstinence led to improvement. The author tested 300 patients with rheumatic disturbances with various types of allergens, and obtained positive reactions in 279 cases. Cereals, meat, and fish accounted for about one-half of the positive reactions. Bacterial proteins were positive in 9 per cent, milk and eggs in 7 per cent. Treatment by hyposensitization as well as elimination was carried out with satisfactory results.

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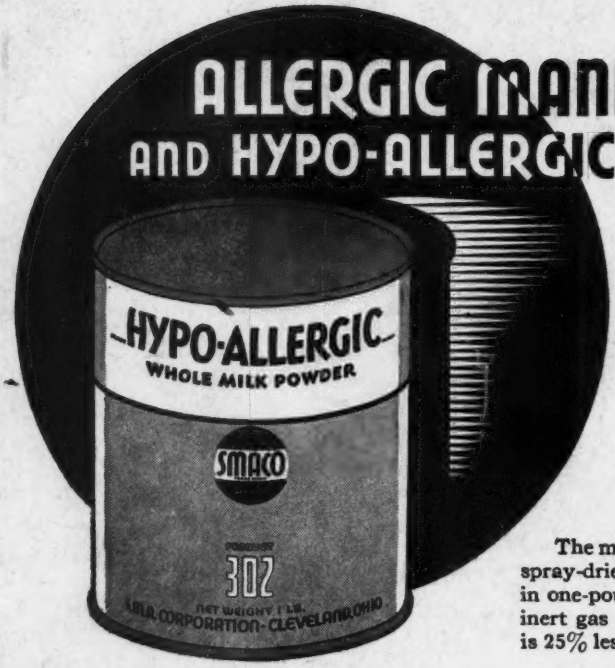

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